IMPORTANCE OF NEURAL FIBROBLASTS IN THE REGENERATION OF NERVE

D. DENNY-BROWN, M.B.
BOSTON

IT IS generally agreed that the regeneration of peripheral nerve is accomplished by the regrowth of axis-cylinders in close relation to the remnants of the Schwann cells of the degenerated nerve. Whether the Schwann bands form a medium favoring active growth or provide simply a passive linear path without obstruction is still debated.[1] Few[2] deny the Schwann cell any part in the process of conduction of the regenerating fiber. There is no doubt, however, that the Schwann nucleus determines the maturation of the myelin sheath at a later stage of restoration. When there has been a breach in continuity in the nerve, the outgrowing axis-cylinder bridges the gap, but the factors which aid or hinder this process are imperfectly understood. These problems have been reviewed at length by Ramón y Cajal[3] and, more recently, by Young[1] and by Weiss.[4] They are of primary importance in all questions relating to nerve grafts, recently reviewed by Sanders,[5] Sanders and Young,[6] Davis and associates,[7] Tarlow and Epstein[8] and Seddon and Holmes.[9]

From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

1. Young, J. Z.: The Functional Repair of Nervous Tissue, Physiol. Rev. **22**:318-374, 1942.

2. Hassin, G. B.: Peripheral Nerves: Anatomic and Physiologic Considerations, Arch. Neurol. & Psychiat. **27**:58-78 (Jan.) 1932.

3. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928.

4. Weiss, P.: The Technology of Nerve Renegeration: A Review; Sutureless Tubulation and Related Methods of Nerve Repair, J. Neurosurg. **1**:400-450, 1944.

5. Sanders, F. K.: The Repair of Large Gaps in the Peripheral Nerves, Brain **65**:281-337, 1942.

6. Sanders, F. K., and Young, J. Z.: The Degeneration and Re-Innervation of Grafted Nerves, J. Anat. **76**:143-166, 1942.

7. Davis, L.; Perret, G.; Hiller, F., and Carroll, W.: Experimental Studies of Peripheral Nerve Injuries: III. A Study of Recovery of Function Following Repair by End-to-End Sutures and Nerve Grafts, Surg., Gynec. & Obst. **80**:35-59, 1945.

8. Tarlow, I. M., and Epstein, J. A.: Nerve Grafts: The Importance of an Adequate Blood Supply, J. Neurosurg. **2**:49-71, 1945.

If the nerve of an animal is severed, the ends retract to some extent. Nevertheless, in the absence of obstruction, a fibrous bridge forms between the two ends. Across this connecting scar sprouts of axis-cylinders make their way to the cut end of the distal nerve. Nageotte [10] discovered that this bridging tissue grew as much from the distal cut end as from the proximal, and in view of its very cellular nature and the tendency of the cells to be associated with fibrils which stained electively with Benda's stain for neuroglia fibrils he claimed its derivation from the Schwann cells of the peripheral segment. He called the outgrowth a "peripheral glioma" and, later,[11] a "Schwannoma." He established the identical nature of the outgrowth from the central cut end, here complicated by the addition of regenerating axis-cylinders. This view has been supported by many investigators, most recently by Masson [12]; Young, Holmes and Sanders [13]; Young,[1] and Weiss.[4] From the beginning Nageotte recognized that fibroblasts became included in the neural scar, and the aim of most methods of grafting or splicing the cut ends of nerves has been to exclude these cells from the union, for the reason that contracting fibrous tissue would eventually strangulate the regenerating nerve fibers.

It is therefore surprising that in 1928 Ramón y Cajal,[3] in his excellent and balanced account of this subject, should state (page 183) that from the second day onward the scar is formed of fibroblasts, which after the third day become arranged in bundles of various sizes, often perpendicular to the wound. He identified the possession of an endocellular Golgi apparatus by these cells, like that described in ordinary fibroblasts, and indicated his belief in their origin from the plasma cells of Unna, which lie around the preexistent blood vessels.

Concerning the origin of the cells that surround the sprouts of the scar from the sixth day after the operation, we must confess that the investigators of the last few years have not dispelled our doubts and that, for us, the ectodermic deviation of these elements is not a demonstrated and irrefutable truth [page 196].[3]

Cajal and others observed that the nerve sprouts travel in the meshes between the cells of the scar and only at a later date are accompanied

9. Seddon, H. J., and Holmes, W.: The Late Condition of Nerve Homografts in Man, Surg., Gynec. & Obst. 79:342-351, 1944.

10. Nageotte, J.: Note sur la présence de fibres névrogliques dans les nerfs périphériques dégénérés, Compt. rend. Soc. de biol. 75:122-124, 1913.

11. Nageotte, J.: Sheaths of the Peripheral Nerves: Nerve Denegeration and Regeneration, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, sect. 5.

12. Masson, P.: Experimental and Spontaneous Schwannomas (Peripheral Gliomas), Am. J. Path. 8:367-388, 1932.

13. Young, J. Z.; Holmes, W., and Sanders, F. K.: Nerve Regeneration: Importance of the Peripheral Stump and the Value of Nerve Grafts, Lancet 2:128-130, 1940.

with Schwann cells, which are oriented along their length and enclose them in cytoplasm. Nageotte [11] described the enclosure of the growing sprout in the scar by the Schwann cell at the seventh day, a phenomenon that appears to be possible only in very short scars. He further described the formation of membranous septums derived from the envelope of the Schwann cell as a primitive endoneurium "which thenceforth grows and becomes vascularized like any connective tissue. Other fibroblasts arrange themselves around the young nerve bunble and among them the lamellated sheath is constructed [page 228]." [11] The fibroblasts were held to penetrate the primitive endoneurium at a late stage. Masson [12] described columns of Schwann cells extending from the interior of an explanted piece of nerve into the new tissue at either end and their subdivision by collagen, which he stated is precipitated around the Schwann cell. Cajal [3] did not offer any description of the development of a perineurium over the regenerated bundle.

In general, the difficulty of establishing good functional union across a gap in nerve increases proportionately to the diameter of the nerve, as well as to the length of the hiatus. Small nerves and the nerves of small animals have an astonishing capacity for attaining good functional union across large gaps without any assistance. Though such a natural bridge also tends to form in larger nerves, the newly regenerated piece of nerve also remains of small size and, consequently, of limited functional value. In human nerve such natural bridges across a gap exceeding about 2 cm. are usually valueless. It is essential, therefore, that the union tissue should allow redevelopment of a nerve of full size. On the basis of experience that the degenerate Schwann tissue of the distal segment of peripheral nerve is the best known conductor of regenerating fibers, the aim of grafting has been to fill the hiatus with such tissue. Though the natural nerve scar tissue is supposed by many to be composed of Schwann cells, it tends to grow laterally and form a mass instead of providing tubular conductors. Even as cement substance between nerve ends its formation is deprecated on account of its high content of collagen. Nerve fibers can certainly grow in neuromas, however; and if more can be learned of factors which lead to their local diffusion and prevent longitudinal development, the healing of neural scars and the bridging of gaps could be improved. The factor usually blamed for failure both of end to end sutures and of nerve grafts is fibrosis.

The origin of intraneural fibrosis is in some doubt. In thick grafts and transplants central necrosis was observed by Maccabruni,[14] Biel-

14. Maccabruni, F.: Der Denegerationsprozess der Nerven bei homoplastischen und heteroplastischen Propfungen, Folia neurobiol. **5:**598-601, 1911.

schowsky and Unger [15] and Bunnell and Boyes,[16] and it was found by Sanders and Young [6] and Davis and associates [7] in some homografts but not in autografts.   On the general pathologic principle that necrosis will progress to fibrosis, some surgeons aim primarily to give the graft a good collateral blood supply either by making a cable of small nerves, with a wider total external surface than that of one large piece, or, recently, by fashioning a fat–areolar tissue flap for the graft.[8]   Others seek to exclude "connective tissue penetration" [4] by sheathing suture lines, or even the whole graft.   In view of the abundant outgrowth of tissue from the cut end of nerve, mentioned earlier, the evidence that connective tissue can grow in at this point appears to be weak.   Further, though vessels grow directly across the nerve ends in simple sutures and into grafts,[17] the supply by this mean is variable, for it was observed to be less in homografts than in autografts.   Tarlow and Epstein [8] demonstrated the defective vascularization of grafts in tantalum sleeves.   They found tension also to be a detrimental factor.

My observations and those of my associates on the effect of percussion on peripheral nerve [18] and on the results of sudden stretching [19] have indicated that rupture of the perineurial sheath of a peripheral nerve bundle leads to consequences more grave than those attending drastic intraperineurial damage.   In perusal of illustrations of Platt,[20] Spielmeyer [21] and others on the pathologic features of neural scars associated with failure of recovery, we have been impressed with the frequent continuity of endoneurial and epineurial fibrosis.   The missing or fragmentary structure is the intermediate sheath, or perineurium. The present investigation began with an attempt to determine the contribution of perineurium to neural scar tissue and led to inquiry as to the degree to which an intact perineurium conserves the process of regeneration.

15. Bielschowsky, M., and Unger, E.: Die Ueberbrückung grosser Nervenlücken: Beiträge zur Kenntnis der Degeneration und Regeneration peripherischer Nerven, J. f. Psychol. u. Neurol. 22:267-318, 1918.

16. Bunnell, S., and Boyes, J. H.: Nerve Grafts, Am. J. Surg. 44:64-75, 1939.

17. Weiss, P.: Nerve Regeneration in the Rat Following Tubular Splicing of Severed Nerves, Arch. Surg. 46:525-547 (April) 1943. Sanders.[5]

18. Denny-Brown, D., and Brenner, C.: The Effect of Percussion of Nerve, J. Neurol., Neurosurg. & Psychiat. 7:76-95, 1944.

19. Denny-Brown, D., and Doherty, M.:   The Effects of Transient Stretching of Peripheral Nerve, Arch. Neurol. & Psychiat. 54:116-129 (Aug.) 1945.

20. Platt, H.: The Surgery of the Peripheral Nerve Injuries of Warfare, Bristol, John Wright & Sons, 1921.

21. Spielmeyer, W.: Zur Klink und Anatomie der Nervenschussverletzungen, Ztschr. f. d. ges. Neurol. u. Psychiat. 29:416-483, 1915.

STRUCTURE OF THE PERINEURIUM

The classic anatomic researches of Key and Retzius [22] established the current conception of the structure of peripheral nerve. These investigators named three supporting structures or sheaths besides the sheath of Schwann with which each individual fiber is provided. Thus, bundles of nerve fibers are bound together by an endoneurium, and each such bundle is surrounded by an outer sheath, or perineurium which is distinct from the loose connective tissue, the epineurium, which holds several neural fasciculi together. Whether the outer membrane covering the myelin belongs to the Schwann cell or is a separate condensation of inner endoneurium (sheath of Plenk and Laidlaw) is disputed.[1] According to Laidlaw,[23] the endoneurial reticulum is continuous with the marginal glia where the nerve roots enter the spinal cord. The perineurium is stated to be continuous with the pia-arachnoid.[22]

In cross section of a nerve trunk each bundle of nerve fibers is seen to be surrounded by its perineurial sheath, which is quite distinct from the epineurium. The collagenous bundles of the latter run longitudinally in the nerve (fig. 1 *B* and *C*), while the fibrils of the perineurium lie at right angles to the nerve bundle. The perineurium also stains less intensely than epineurium with eosin or with phloxine. The nuclei are interspersed between the collagenous bundles and are more easily studied in tangential section. They are then found to be large and oval, without a nucleolus in their resting stage. In maceration, they are found to be arranged in concentric layers of lamellas, separated by a collagenous fibrillar membrane; hence the old name "lamellar sheath." The perineurium is continuous with the sheaths of encapsulated end organs, such as the pacinian corpuscle, the lamellated outer structure of which is a form of specialized perineurium (Schäfer[24]). The flattened "epithelioid" laminas of cells thus enclose potential spaces surrounding the nerve bunble. Injection material, especially if oily in nature, can be introduced into or under the perineurium and be made to run considerable distances under slight pressure, passing into the subarachnoid space, when the injection is made into nerve roots, or into the capsules of muscle spindles, pacinian corpuscles, and so forth, when the injection is made in a peripheral direction.[25]

22. Key, A., and Retzius, G.: Studien in der Anatomie des Nervensystems und des Bindegewebes, Stockholm, Norstedt och Söner, 1876.

23. Laidlaw, G.: Silver Staining of the Endoneurial Fibers of the Cerebrospinal Nerves, Am. J. Path. **6**:435-443, 1930.

24. Schäfer, E. A.: Text-Book of Microscopic Anatomy, in Quain's Elements of Anatomy, London, Longmans, Green & Co., 1912, vol. 2, pt. 1.

25. Funaoka, S., and Watanabe, M.: Untersuchungen über das periphere Nervensystem, Folia anat. japon. **11**:37-39, 1933. Key and Retzius.[22] Watanabe,
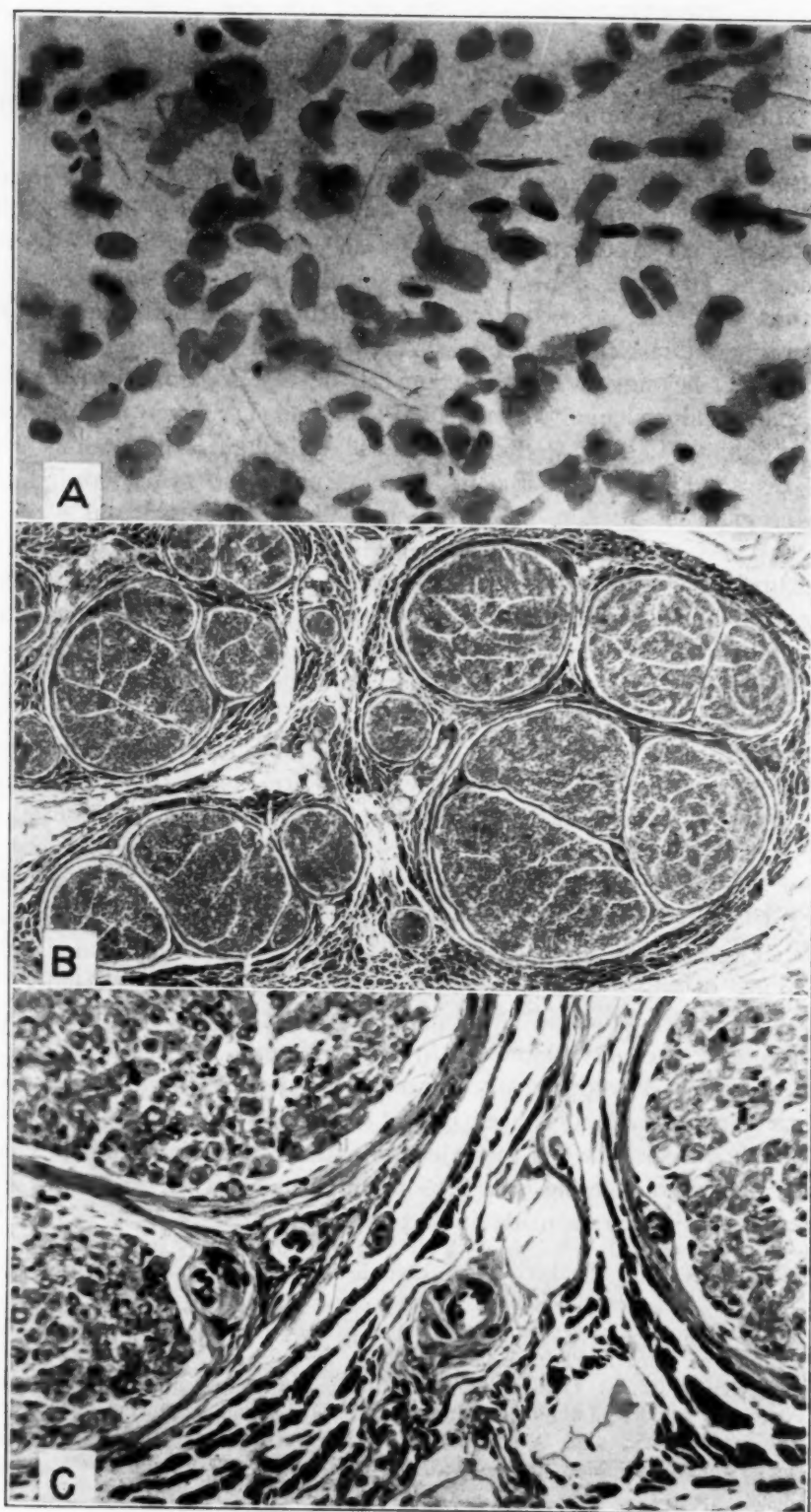
(See legend on opposite page)

When segments of nerve are rendered edematous, as by compression through ligature or other means or by partial ischemia,[26] fluid collects under the perineurium, separating it from the nerve bundle and the endoneurium. Frequently the lamellas of the sheath then become separated by layers of fluid, and the pavement of cells is clearly defined (fig. 1 *A*). The large pale nuclei closely resemble those of peritoneal mesothelium. The perineurial space of digital nerves, and of nerves passing through areas of considerable movement (wrist, ulnar groove), appears regularly to contain fluid, whereas that of more proximal nerve trunks does not. The perineurium forms a barrier to inflammatory processes, for my associates and I have commonly observed that the cellular reaction external to the sheath may be intensely polymorphonuclear whereas that internal to it is mononuclear. This striking barrier effect is seen in the reaction to freezing, in the reaction to traumatic hemorrhage of both sheaths and in certain kinds of neuritis, especially leprosy, of which I shall report elsewhere.

In conditions of localized inflammatory reaction of the nerve, as in response to freezing a segment of it, edematous fluid collected under the perineurium. Two special types of cell can then be seen to be shed from the perineurial lining. One is the flat macrophage, with eccentric, bean-shaped, pale nucleus and a central pale area in its cytoplasm; the other is a spindle-shaped fibroblast, with plump branched processes and an oval longitudinal nucleus.

The perineurium, therefore, may be regarded as a natural barrier for peripheral nerve, arranged in a multilayered sheathing enclosing

M.: Injektionversuche in die sensiblen Nervenendapparate, Arb. a. d. dritten Abt. d. anat. Inst. d. Kaiserlich. Univ. Kyoto, 1935, ser. A, no. 4, pp. 57-64.

26. Denny-Brown, D., and Brenner, C.: Lesion in Peripheral Nerve Resulting from Compression by Spring Clip, Arch. Neurol. & Psychiat. **52**:1-19 (July) 1944.

Explanation of Figure 1

Fig. 1.—*A*, perineurial membrane of the sciatic nerve of the cat, edematous as a result of transitory compression 1 cm. proximal to the level of section. The tangential section shows the nuclear content of the lamellas between two nerve bundles, where epineurium is lacking. The large pale nuclei often overlap, for they belong to different layers of the membrane. Note also the darker, smaller, oval nuclei, sometimes pointed at one end.

In this figure, and in all figures showing nerves sectioned longitudinally, the proximal part of the nerve is to the left of the figure. All the tissues are from the sciatic or the ulnar nerve of the cat, with the exception of those shown in *B* and *C* of this figure.

B, transverse section of the human sciatic nerve. Hematoxylin and eosin stain.

C, higher magnification of the upper left corner of *B*, showing the laminated perineurium and its nuclei, with small blood vessels, and the strands of epineurium in cross section. The space under the perineurium is an artefact due to shrinkage.

potential spaces and loosely attached to the endoneurium by fibroblastic processes, which are prominent when edema first forms but later fall back to line a smooth-walled space. Vessels entering the nerve bundle carry a sheet of perineurium into the center of the nerve bundle, where it appears to be continuous with the endoneurium. The cells with large pale nuclei can be followed along the vessels within the neural bundle, where they are usually called endoneurial cells (Cajal [3]). By splitting the perineurium and grasping the nerve fibers with fine forceps through the opening, one finds that the nerve can be moved up and down within its sheath with some freedom. I am not able to bring any additional evidence to the disputed question of the ectodermal or endodermal origin of the endoneurium or the perineurium and accept the general opinion that both are probably specialized fibroblastic tissues of mesodermal origin.

PROCESS OF NATURAL REPAIR OF LOSS OF NERVE SUBSTANCE

Within a few hours after section of a peripheral nerve, when the severed ends are left some distance apart, exuberant sprouting of cells from each cut end begins. I have already indicated the opinion of Nageotte and Cajal with regard to this process and would further cite the excellent studies of Young, Holmes and Sanders [13] on the rate of development of the cellular masses (neuroma on the central end, "schannoma" on the peripheral end) and of Ingebrightsen [27] on the phenomenon as observed in tissue culture. These authors subscribed to Nageotte's view that the cells are Schwann cells, though Holmes and Young [28] (page 72) added that "the fibrous tissue of the perineurium and epineurium grows out with even greater activity than the Schwann tissue." From the observations of my associates and myself, I would add the following features: First, the swellings are solid and lack the tissue spaces of the parent nerve, now distended by macrophages, with or without edematous reaction. Second, the cells nearest the columns of "Schwann cells" at the cut end often lie transversely or obliquely to these, and not in direct alinement. The perineurium becomes thickened at and near its cut edge, and from here rows of cells stream in line into the main mass. The character of these cells does not appear to me to differ in any way from that of the cells that make up the bulk of the mass. Last, when nerve fibers from the proximal stump penetrate the proximal cell mass, and, also, when they reach the distal stump, they travel on the surface of

27. Ingebrightsen, R.: A Contribution to the Biology of Peripheral Nerves in Transplantation: II. Life of Peripheral Nerves of Mammals in Plasma, J. Exper. Med. 23:251-264, 1916.

28. Holmes, W., and Young, J. Z.: Nerve Regeneration After Immediate and Delayed Suture, J. Anat. 77:63-96, 1942.

the cells, as noted by Cajal, and not in the cytoplasm, as they do in many of the Schwann bands of the peripheral nerve, and as was clearly observed by Bielschowsky and Valentin [29] in the Schwann bands after freezing and by Brenner and me [17] in the pseudoneuroma after percussion. Holmes and Young [28] commented on the difficulty in distinguishing the nuclei of Schwann cells and those of fibroblasts, stressing the tendency of the former to form strands and of the latter to show irregular outline. The difficulty is increased by the tendency of both nuclei to become more circular and to show a prominent nucleolus when first activated. My colleagues and I have found that Mallory's phosphotungstic acid hematoxylin stain (especially Peers's [30] modification) gave fairly sharp differentiation. This regularly stains the Schwann nucleus and some large connective tissue nuclei a diffuse deep blue. The great increase in nuclei in cell columns of both stumps of the sectioned sciatic nerve in the cat is due to the presence of large numbers of plump oval nuclei, which either do not take the phosphotungstic acid hematoxylin stain or show only a faint blue nuclear membrane. The situation is clearest in the central stump, where the nerve fibers are often separated by edema. A few large pale oval nuclei of the type called "fixed connective tissue cell" by Doinikow,[31] are found free in the tissue spaces, particularly near blood vessels. The very small, rodlike Schwann nuclei lie closely applied to myelin or to nonmedullated nerve fibers. Both these types of nuclei stand out sharply with the blue phosphotungstic acid hematoxylin stain (fig. 2 *B*), without any transitional elements. The large numbers of plump oval nuclei with a prominent nucleolus which make up the cell columns containing regenerating nerve fibers seen in sections stained with hematoxylin and eosin or with the Nissl method (fig. 2 *A*) do not take the phosphotungstic acid hematoxylin stain except for blue coloration of the nuclear membrane when the stain is intense. The stain colors the collagen which enmeshes these nuclei, and with critical staining after fixation in Zenker's fluid the proliferating cells with unstained nuclei clearly have fibroglia, which lies within the collagen framework. The nuclear membrane and nucleoli then also stain blue. The cells appear to be separate and not to form a syncytium.

The phosphotungstic acid hematoxylin stain further reveals that the neural scar tissue emerging from either the proximal or the distal

29. Bielschowsky, M., and Valentin, B.: Die histologischen Veränderungen in durchfrorenen Nervenstrecken, J. f. Psychol. u. Neurol. **29**:133-152, 1922.

30. Peers, J.: A Modification of Mallory's Phosphotungstic Acid-Hematoxylin Stain for Formaldehyde-Fixed Tissues, Arch. Path. **32**:446-449 (Sept.) 1941.

31. Doinikow, B.: Beiträge zur Histologie und Histopathologie des peripheren Nerven, in von Nissl, F., and Alzheimer, A.: Histologie und Histopathologie, Jena, G. Fischer, 1911, vol. 4, pp. 445-630.
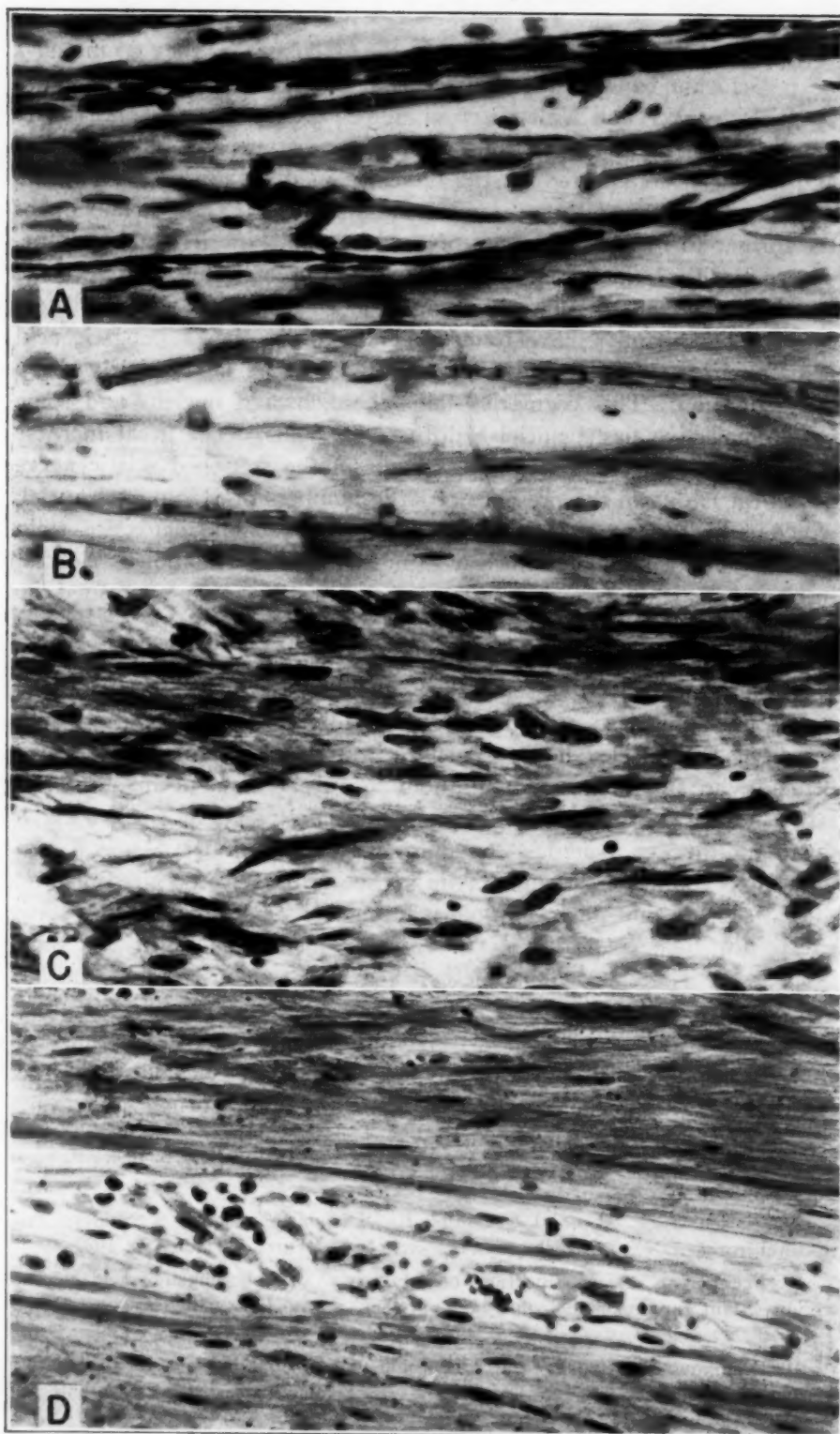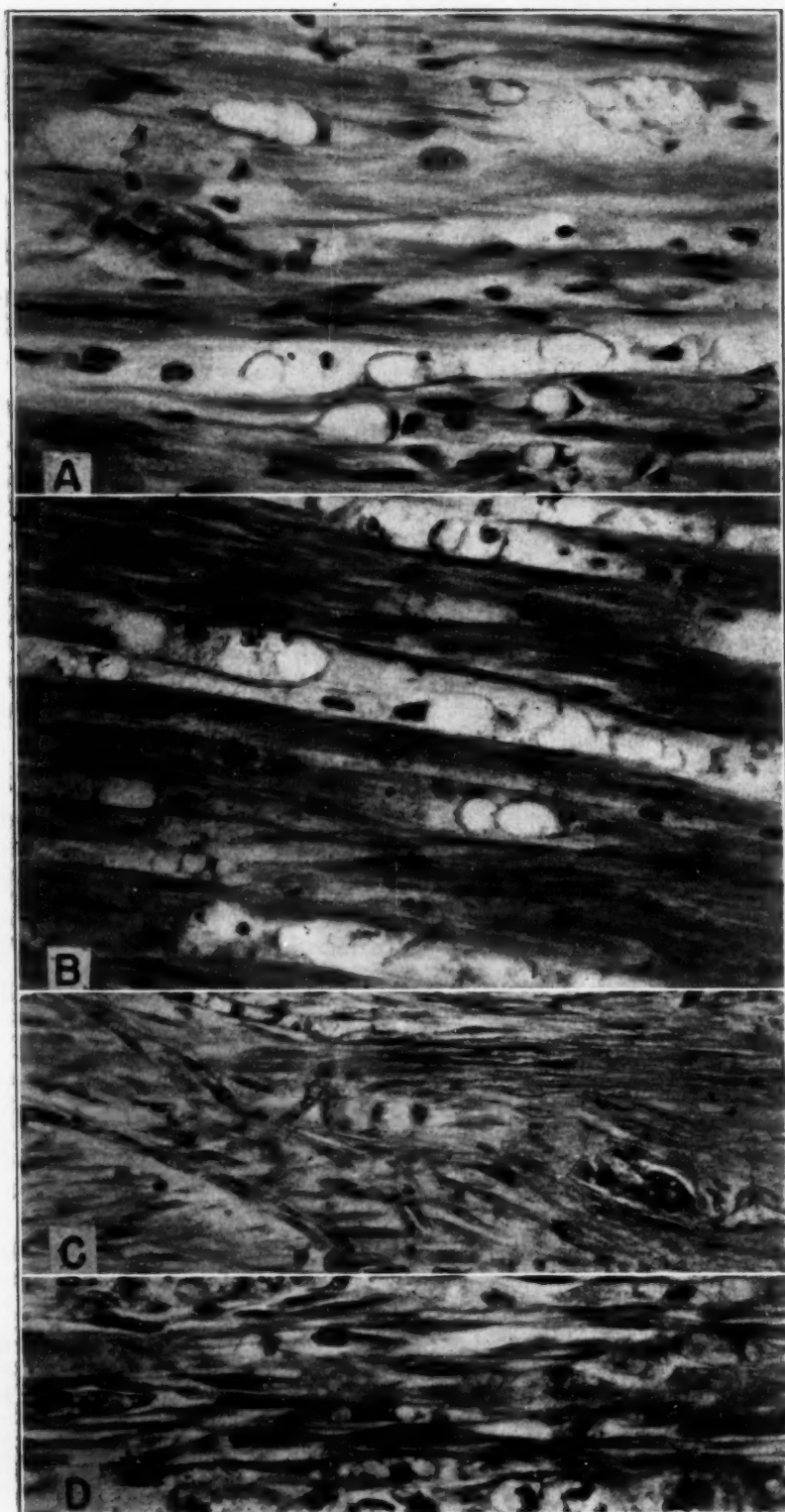
(See legend on opposite page)

stump contains few, if any, of the blue, rod-shaped nuclei until invaded by nerve fibers (fig. 2 *D*). It is difficult to maintain a peripheral stump entirely free from nerve fibers, and the few nuclei found were reasonably accounted for by the few nerve fibers in the "aneuritic neuromas." The large oval "fixed connective tissue" nuclei are scattered singly or in small groups near blood vessels or in more open spaces. The large numbers of plump oval nuclei which form the cell columns of the growing tissue do not take the stain, though their dark nucleoli stand out prominently (fig. 2 *D*). A section stained with Masson's trichrome method reveals that all three groups are equally stained (fig. 2 *C*). By these criteria, the "schwannoma" and "neuroma," before the entry of nerve fibers, are composed of cells differing from Schwann cells.

Indeed, by these criteria there is a paucity of Schwann nuclei at both the central and the peripheral cut end of nerve for the first 3 to 5 mm. (fig. 3 *A* and *B*). The characteristic thread of cytoplasm of each Schwann cell in the bands of Büngner of the main distal degenerated portion of the nerve is found to shrink progressively as one passes from the main trunk of the distal piece of peripheral nerve into the first 5 mm. of the peripheral stump. The few remaining rod-shaped cells in the stump itself did not have processes (fig. 3 *B*). In the same region of transition, more and more plump nuclei staining poorly with phosphotungstic acid hematoxylin occupy the columns. In critical staining the nuclear membrane takes the stain, and fibroglia is present (fig. 3 *D*). Some of the nuclei are narrow, but these have sharp ends. Either the Schwann nucleus undergoes complete metamorphosis or it is replaced. My associates and I have considered the possibility that the staining characteristics alter with regeneration. A study of scars of different ages revealed that the fresh nuclei shaped like narrow, blunt rods and showing frequent mitoses enter the scar only when accompanying the regenerating nerve fibers and follow the course of such fibers. In this migration the Schwann nuclei retain

---

Explanation of Figure 2

Fig. 2.—*A*, section from the edematous region of the central stump of a sciatic nerve divided seventy-five days before. Fixation in solution of formaldehyde U.S.P.; Gros-Bielschowsky method, counterstained with hematoxylin and eosin. *B*, section from the same region as that shown in *A*, stained with phosphotungstic acid hematoxylin (Peers's modification). *C*, section from the scar tissue bridging the two stumps twenty-one days after section of the sciatic nerve. Note the two Schwann nuclei in the upper central field. Fixation in Zenker fluid; Masson's trichrome method. *D*, section from the same region as that shown in *C*, stained with phosphotungstic acid hematoxylin. A small vessel with mononuclear cells occupies the lower central field. Note the three Schwann nuclei above this. The numerous black dots are nucleoli of unstained fibroblastic nuclei. The nuclear membranes and the fibroglia are not stained. Note the two Schwann nuclei lying above the vessel and histiocytes.

(See legend on opposite page)

their peculiarity of staining and form. The oblique separation of freshly divided nuclei is especially characteristic. Further, when myelination begins, most such nuclei are found embedded in a myelin segment. We have not found such Schwann nuclei closely embedded in collagen.

The nuclei of the cells composing the "junctional tissue" or scar are variable in size and shape, being more sharp pointed and oat shaped when the linear arrangement and collagen lines appear to indicate tension and more plump and oval when they are lying free in a tissue space. They are commonly rounded at one end and slightly sharper at the other. One or two nucleoli are prominent. In view of the intense proliferation both within the nerve stumps and in the scar, it is suprising to find little evident mitosis. Many of the oval nuclei show a prominent nucleolus at either pole with a constriction in the middle, and this has undoubtedly led many authors to consider that these cells divide amitotically.[12] Careful inspection of a phosphotungstic acid hematoxylin preparation reveals, however, that a typical metaphase does occur, though the clusters of chromosomes are very small, and at first sight look like ragged nucleoli. They are about half the size of the spindle of the smallest Schwann cells. In the more common prophase the nucleus is tigroid in appearance.

These nuclei can be traced back from the scar into the cell columns of the nerve stumps, where they are in active division, as indicated by Masson.[12] They can, however, be traced farther into the main trunk of the degenerated peripheral segment, where, in much smaller numbers, they are found in characteristic form, lying on the surface of the columns of Schwann cells (fig. 3 D). The nucleus of the resting cell frequently stains a light diffuse blue with phosphotungstic acid hematoxylin and may have no nucleolus, but is still much paler than the

---

EXPLANATION OF FIGURE 3

Fig. 3.—A, section from the distal stump of a divided sciatic nerve twenty-one days after section, 2 mm. from the level of section. Note the large, pale, oval or circular nuclei and the numerous darker, smaller oval or pointed nuclei accompanying the collagenous bands. Some rod-shaped Schwann nuclei with blunt ends are seen near the lower left and the upper right corner. Fixation in Zenker fluid; Masson trichrome stain.

B, tissue from a section near that shown in A, stained with phosphotungstic acid hematoxylin. The dark, diffusely stained nuclei in the cell columns belong to Schwann cells. The irregular nuclei belong to phagocytes. The fibroblastic nuclei are represented only by the nucleolus and a faint outline.

C, junctional tissue between the nerve ends of the sciatic nerve, frozen for three and a half minutes and sectioned in the frozen segment sixteen days earlier. Most of the cells show fibroglia. None of the nuclei stain diffusely. Fixation in Zenker fluid; phosphotungstic acid hematoxylin stain.

D, critical staining of distal nerve stump, 3 mm. from the end. Two Schwann cells lie in the lower middle of the figure. The fibroblasts have well developed fibroglia processes, which branch in clefts between collagen fibers. Fixation in Zenker fluid; paraffin embedding; phosphotungstic acid hematoxylin stain.

Schwann nucleus. The plump oval nucleus often lies slightly oblique to the longitudinally oriented Schwann bands. Mitosis is common. These cells are here identical with those which Doinikow [31] called endoneurial cells. Amitotic division was also noted by Doinikow, but we found the same small mitotic spindles. These elements differ from the large flat cells with broad nuclei (endoneurial cells of Cajal, fixed connective tissue cells of Doinikow) lying near blood vessels in being more oval, sometimes even sharp at the end, and having two plump stems of cytoplasm. Brenner and I [18] noted that they proliferated rapidly and became wrapped around nerve fibers injured by percussion.

Observation of the selective necrosis of nerve induced by freezing nerve [32] indicated a further possible means of separating the contributions made by Schwann cells and perineurium to the scar, for Schwann cells were found to be extremely sensitive to freezing. A segment of sciatic nerve in the cat was frozen hard for three and a half minutes, thawed with warm saline solution and then sectioned in the middle of the previously frozen segment and left for two weeks. The two nerve ends were found to be joined by the usual fibrous band at the end of this period. Section showed that at the end of the stumps no Schwann cells survived, though abundant phagocytes filled with fat poured from the cut face of the nerve. The epineurium had undergone proliferation and contributed fibroblasts to the scar. The greater part of the scar, however, was made up of columns of cells streaming from thickened perineurium directly into the tensile scar and holding the nerve ends together. Endoneurial cells of identical kind also contributed. A diffuse brown collagen surrounded both the perineurial and the endoneurial cells and their derivative tissues, differing from the red strands which accompanied epineurial fibroblasts. All these cells had fibroglia, and those derived from perineurium and endoneurium had nuclei which failed to stain with phosphotungstic acid hematoxylin or showed only the nuclear membrane and the nucleolus (fig. 3 C). The scar thus formed appeared to be identical with that normally found.

The formation of increased numbers of both large oval and moderate-sized plump nuclei could be traced from perineurium, as well as from residual strands of endoneurium. Inspection of flat preparations of perineurium reveals that they are there also normally present in small numbers (fig. 1 A), preserving the same differences which distinguish them in endoneurium. One may conclude, therefore, that the cellular proliferation in nerve following injury and leading to scar formation is related to a type of cell present in the perineurium and

32. Denny-Brown, D.; Adams, R. D.; Brenner, C., and Doherty, M. M.: The Pathology of Injury to Nerve Induced by Cold, J. Neuropath. & Exper. Neurol., to be published.

endoneurium which has the characteristics of a fibroblast but which
differs from the epineurial fibroblast in at least two respects, namely,
a tendency to form a diffuse type of collagen and absence of diffuse
nuclear staining with phosphotungstic acid hematoxylin. The cells also
tend to become oriented in parallel rows, especially when under tension.
They appear to be identical with the palisaded perineurial fibroblasts of
Mallory.[33]

REGENERATION OF NERVE WITHIN INTACT PERINEURIUM

As a corollary to the conclusion reached earlier, it was logical next
to inquire as to the fate of a nerve sectioned and left within its natural
perineurial sheath. The ulnar nerve, being in the greater part of its
humeral segment a single homogeneous fasciculus in the cat, was selected.
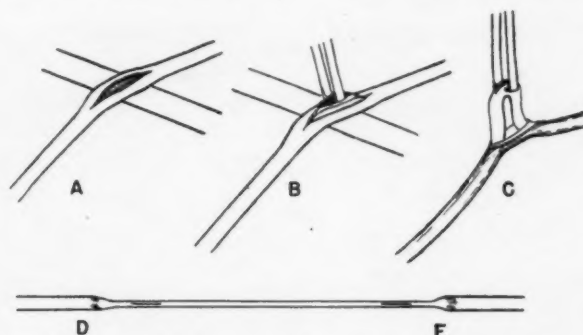The nerve was exposed, drawn taut and a longitudinal incision 5 to

Fig. 4.—Method of extraction of the contents of the perineurial sheath
described in the text.

7 mm. in length made into the fasciculus in its distal third (fig. 4 A).
The edges of the incision gaped apart, and the cut surfaces of the nerve
fibers were grasped in a fine-toothed forceps, care being taken to avoid
the cut edges of the perineurium (fig. 4 B). By traction the nerve
bundle was herniated through the slit in the perineurium, which was
peeled back gently. A firmer grip was then taken of the whole bundle
(fig. 4 C). The loop of nerve fibers was then cut at its distal end.
A similar incision was made 2 to 3 cm. proximally, and the loop of
nerve pulled out was sectioned at its proximal end after pulling back
the perineurium as far as possible. By gentle traction on the upper
loop the intervening segment of nerve fibers was now pulled out of the
perineurium, leaving a membranous tube with two slit-shaped incisions
(fig. 4 D and E). In some experiments three incisions were made,
the nerve being withdrawn in two segments, so as to avoid undue trac-

33. Mallory, F. B.: The Type Cell of the So-Called Dural Endothelioma,
J. M. Research **41**:349-364, 1919-1920.
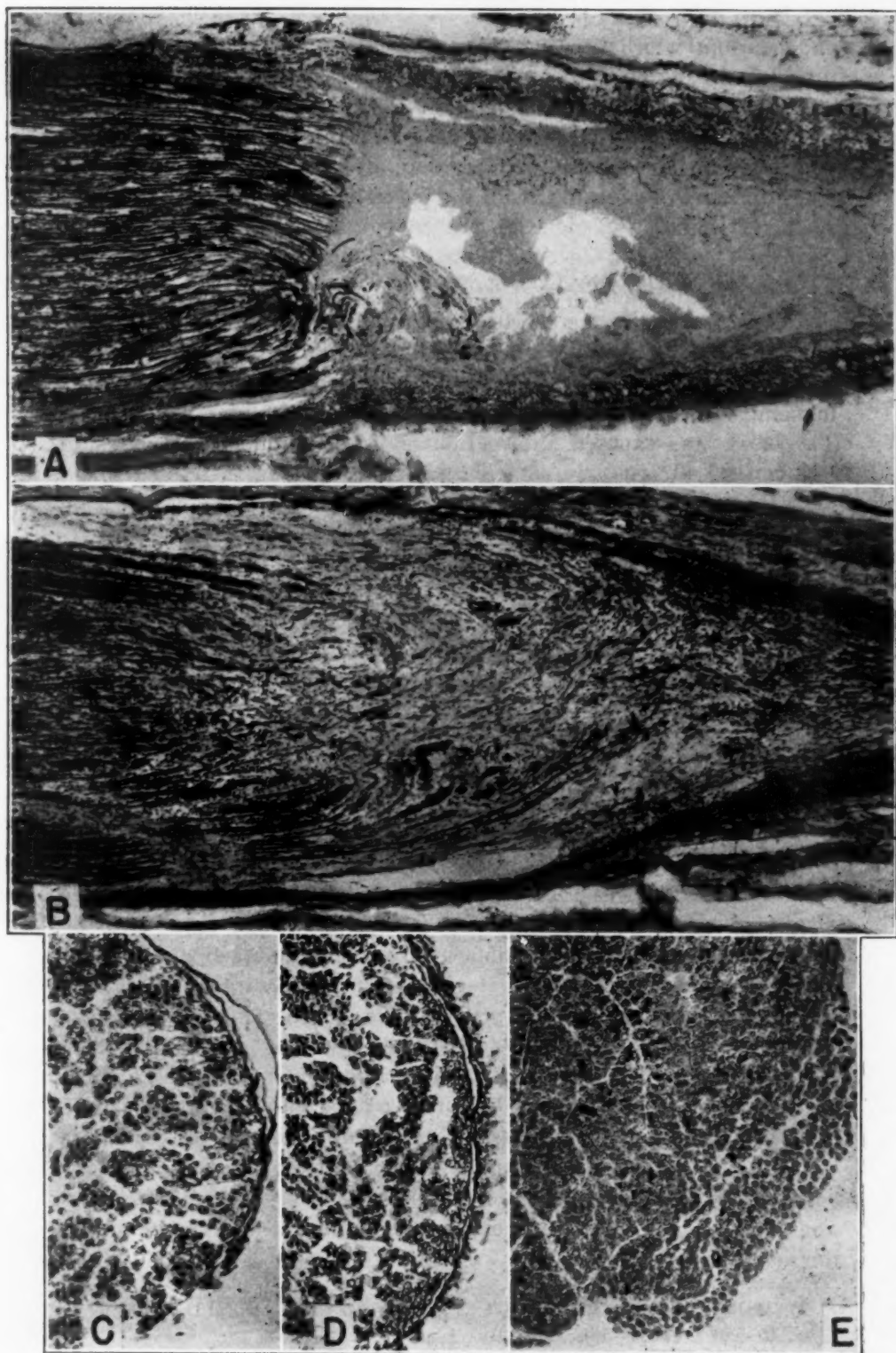
(See legend on opposite page)

tion by pulling a long piece from one end. It is important that the perineurium should be handled as little as possible and not ruptured. In large nerves with more epineurium it is necessary to be sure that nerve fibers deep in the incision are alone caught by the forceps and that the nerve bundle as it is pulled forth sheds all the perineurial sheath in the first pull, so that thereafter it emerges smooth and glistening, without any trace of blood vessels or fibrous tags. Transverse section of this piece of nerve thus pulled out usually showed one or two adherent lamellas (fig. 5 C) and was sometimes completely denuded (fig. 5 E). If the nerve is pulled too hard or is insufficiently separated, the whole perineurium, with tags of epineurium, may be removed (fig. 5 D). Only by such section can one be sure that the perineurium itself is not also dragged forth.

The condition of the central stump, surrounded by the intact perineurial tube, twelve hours after the operation is shown in figure 5 A, in which the retraction of the nerve fibers, the ends of which had fragmented, will be seen. The perineurial sheath had frayed into separate laminas and, with the epineurium, was the seat of a mild inflammatory reaction. There was a very slight hemorrhage. A section of the center of the perineurial tube after the same period showed that the walls had collapsed together, obliterating the central lumen. The perineurial cells and their lamellas had already swollen to form a laminated solid band.

The procedure just outlined was carried out at open operation with the animal under deep pentobarbital anesthesia, leaving a 3 cm. gap in the nerve with intact perineurium, and as a control the left ulnar nerve was excised so as to leave a 3 cm. gap between the cut ends. After an interval of twenty-eight days the nerves were exposed with the animal under pentobarbital anesthesia. Electrical stimulation above and below the gap elicited no movement on either side. Whereas the nerve ends on the left side (total excision) now each presented a large neuroma, connected by a fibrous band densely adherent to muscular and other neighboring tissues, the nerve on the right side remained thin and as freely movable as a normal ulnar nerve. There was a slight enlargement of the former proximal nerve fasciculus, which tapered down to a fibrous cord 1 cm. long, and distally this

EXPLANATION OF FIGURE 5

Fig. 5.—A, proximal stump of ulnar nerve twelve hours after subperineurial excision. Gros-Bielschowsky method; counterstained with hematoxylin and eosin.
B, proximal stump of ulnar nerve, twenty-eight days after subperineurial excision; Gros-Bielschowsky method; cresyl violet stain.
C and D, sections of avulsed portion of the ulnar nerve from various experiments mentioned in the text. Hematoxylin and eosin stain.
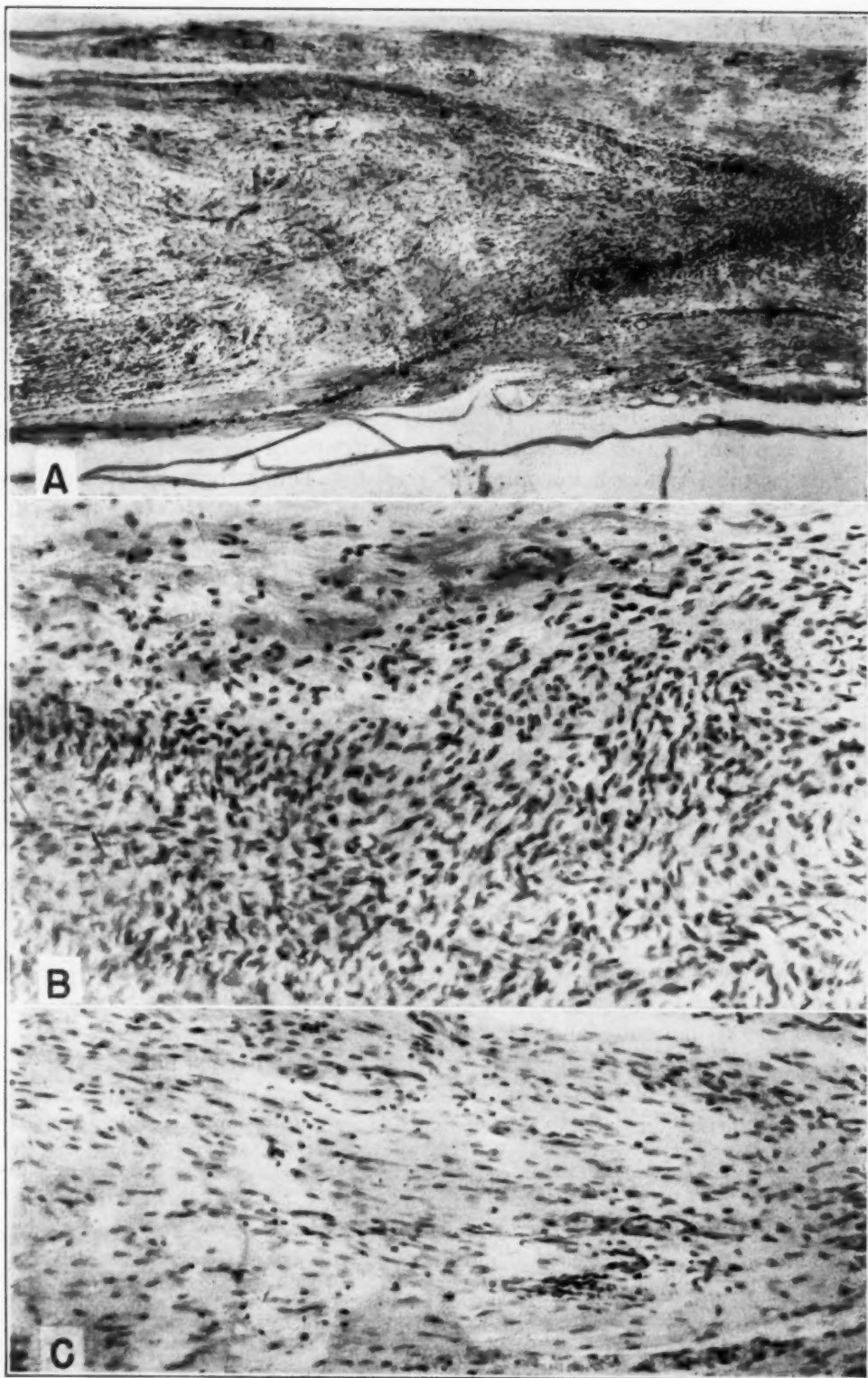
(See legend on opposite page)

tapered gradually to the normal diameter of the nerve without distal enlargement. Section of the proximal extremity of the perineurial tube revealed that the slight enlargement was caused by dilatation of the tissue spaces of the nerve at and just beyond the original point of section (fig. 5 *B*). The perineurial sheath had formed a cone, enclosing growing nerve fibers. This edematous central nerve end showed intense proliferation of endoneurial fibroblastic nuclei with elongation of axis-cylinders, many of which crossed and recrossed and a few of which had just penetrated the tip of the wedge. These fibers were accompanied with moderately numerous Schwann nuclei, resembling the condition shown in figure 2 *A*. There was intense cellular proliferation at the distal extremity of the perineurial cone (fig. 6 *A*), which lay 5.5 mm. from the level of original section; and large numbers of cells with pale oval nuclei and branched, pale cytoplasm in a loose spongy tissue filled the center of the conductor beyond (fig. 6 *B*), becoming distally more sparse (fig. 6 *C*) but extending as a cellular cord to meet a cone-shaped extension of perineurial cells extending medially for 3.5 mm. from the distal stump (fig. 7 *A*). Loose cellular fibroblastic laminas extended from the central cord to the surface, where more dense epineurial strands formed an outer layer (fig. 6 *B*). Small blood vessels permeated the whole tissue.

There was no difference between the nuclei of the distal cell mass and those which extended distally from the central perineurial cone. In sections stained for collagen with Mallory's phosphotungstic acid hematoxylin (figs. 7 *B* and *C*) these cells were found to have the staining characteristic of those we have identified as perineurial and endoneurial fibroblasts in neural scars. In addition, it was seen that, whereas both cellular cones were lightly and diffusely collagenized, funnel-shaped collagenous septums appeared to spring from the walls of the tube as lamellar bands and strands over the intermediate section. In places the central columns of cells were subdivided longitudinally by such a partition. In addition, a collagenous deposit had extended into the first 2 mm. of the distal stump, as is usual in all nerve stumps.

At the four week stage, therefore, the situation represented a collapse of the original perineurial tube with proximal reopening by an active growth tip of nerve fibers covered by Schwann cells and having the

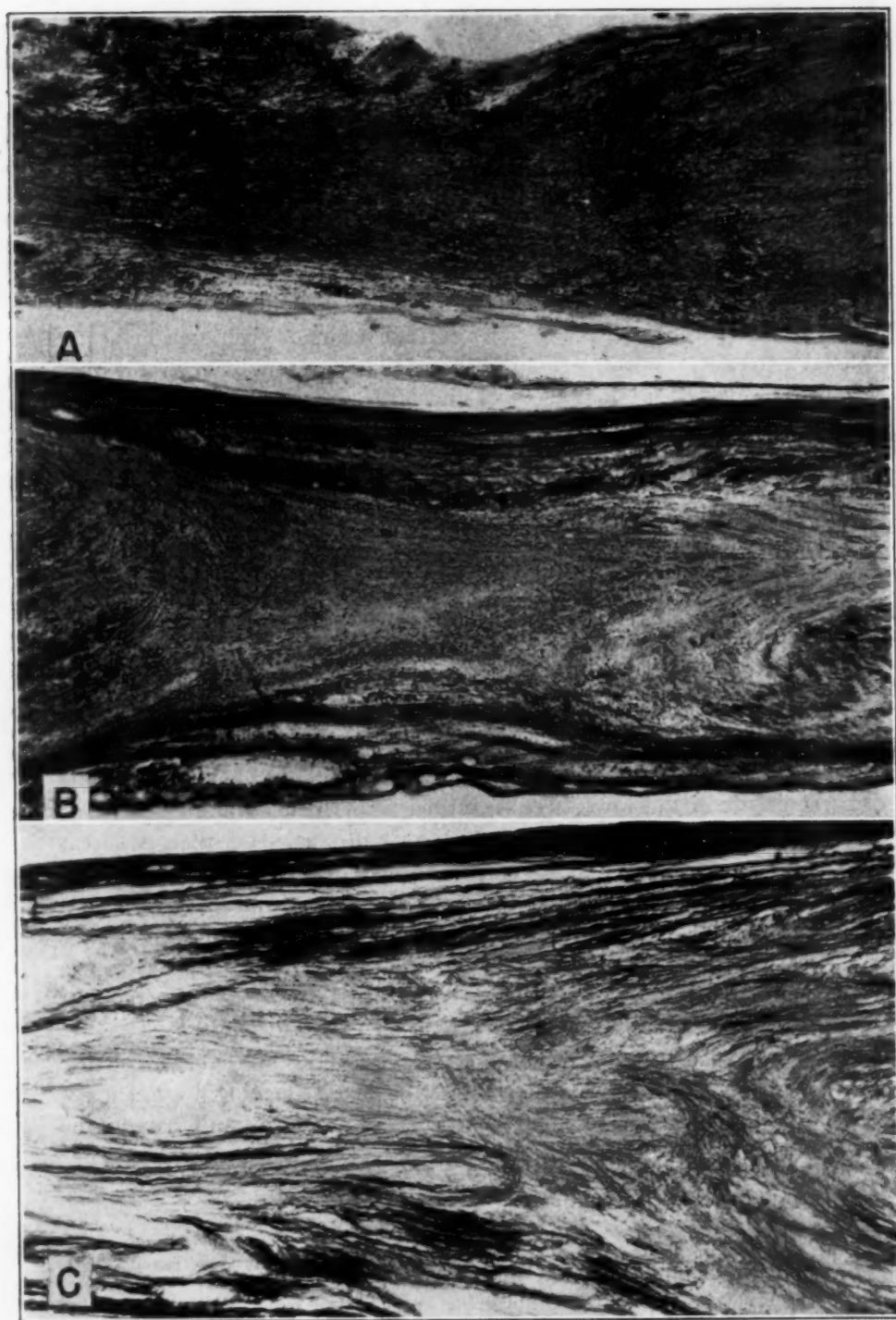---

EXPLANATION OF FIGURE 6

Fig. 6.—Proximal stump of ulnar nerve, as shown in figure 5 *B*, twenty-eight days after subperineurial excision. Hematoxylin-eosin stain.

B, higher magnification of the cellular apex to the right of the point from which *A* was taken.

C, core of the perineurial connection about 1 cm. distal to the point from which *B* was taken.

(See legend on opposite page)

appearance of a fluid wedge. There was much spiraling of the nerve fibers in the edema·proximal to this wedge but no true neuroma formation. The cone of the connecting scar appeared to consist of activated fibroblasts without Schwann cells. There were few Schwann cells in the first 2 mm. of the peripheral stump.

LONG TERM SURVIVAL AFTER SUBPERINEURIAL EXCISION OF ULNAR NERVE

In another experiment, the fibers of the right ulnar nerve were similarly excised for 3 cm., leaving the perineurium. The left ulnar nerve was sectioned in three places, leaving two pieces 1.1 and 1.2 cm. long, respectively, in a gap of 3 cm. There were thus three gaps of 0.5, 0.1 and 0.1 cm., respectively, in the control nerve. After an interval of ninety-nine days the nerves were explored with the animal under anesthesia. The nerve on the left (control) side presented three large neuromas, which with the intervening pieces of nerve were densely adherent to the neighboring vessels and muscles. On the right side the ulnar nerve appeared thin for about 2 cm., and two slight enlargements marked the site of former avulsion of its contents (fig. 11 *A*). No adhesions of any kind were present. Electrical stimulation of the control ulnar nerve above the triple lesion excited a weak (25 per cent) flexion of the wrist with weak protrusion of the radial claw. Stimulation of the right ulnar nerve excited moderate (50 per cent) flexion of the wrist, with strong protrusion of the radial claw.

Sections of the left ulnar nerve showed the appearance characteristic of neuromatous neural scars. The right ulnar nerve was sectioned transversely at the junction of the upper and the middle third and of the middle and the lower third and was stained with osmic acid. This preparation showed one small medullated branch surrounded by perineurial sheaths at each level. This appeared to be a small subsidiary bundle missed in the original "pulling" of the nerve. The remainder of the section was fibrous, with numerous scattered nerve bundles, each in a stage of advanced myelination.

EXPLANATION OF FIGURE 7

Fig. 7.—*A*, section from the same experiment as the sections in figure 6, the distal stump of the nerve being shown on the right with dense cellular mass · extending medially as a cone into the perineurium. Cresyl violet stain.

B, section from the same experiment, the proximal cellular cone being stained with phosphotungstic acid hematoxylin (Peers's modification). The tip of the cone lies at the junction of the right and the middle third. No Schwann nuclei lie distal to this.

C, section from the same experiment, showing the distal cone stained with phosphotungstic acid hematoxylin.
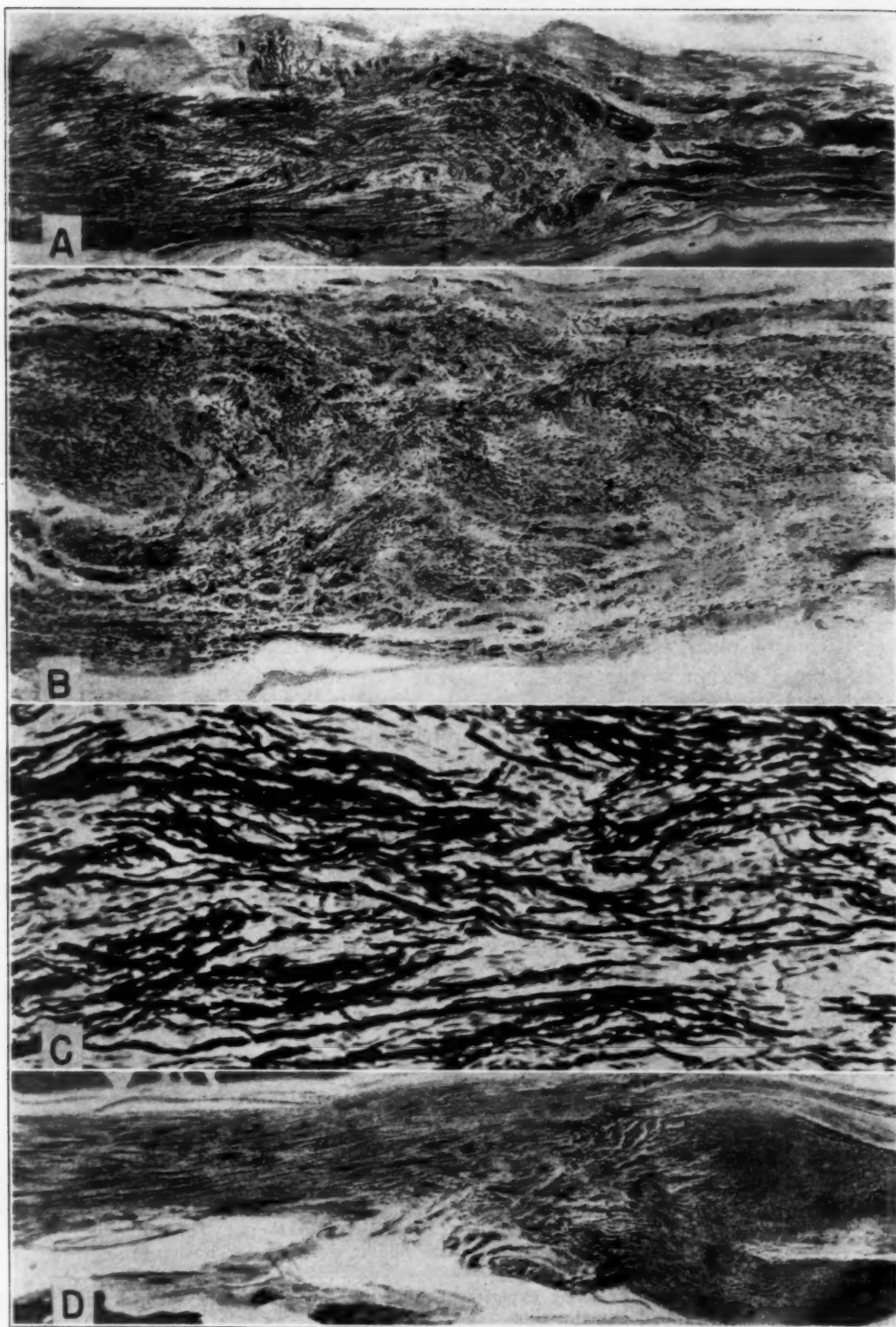
(See legend on opposite page)

Longitudinal sections showed that nerve fibers had advanced through the entire length of the area of excision (fig. 8). In the region of the original proximal section, Perroncito spirals were frequent but of loose structure and passed by a heavy regeneration of nerve fibers, which coursed as several bundles 3.5 mm. after leaving a proximal cone (fig. 8 *A*). They then coursed as one bundle for 2 mm. At this level some septal partition appeared. The nerve then continued as separate bundles partitioned by thin septums until, 4 mm. from the distal nerve end, still recognizable by its fatty phagocytes, they met the apex of the solid mass of cells projecting medially from the peripheral segment (fig. 8 *D*). At this point the axis-cylinders continued their peripheral course, running separately in the interstices between the fibroblastic cells until the cone of the peripheral stump was attained. The nerve fibers took oblique and intertwining courses throughout the long passage (fig. 8 *C*), but none was seen to turn back and no neuromatous confusion of direction was observed.

The distal cone was asymmetric (fig. 8 *D*), having grown laterally to one side in a neuromatous bulge, which was attributed to part of the entire perineurium having been withdrawn in the original pulling and being present with the avulsed nerve at this end (fig. 5 *D*). The bundles of nerve fibers had, however, by-passed this region and made satisfactory connection. Many fibers had myelinated throughout their length, and many more had matured in the peripheral nerve than in the control limb; but the structure of the nerve which had grown through the perineurial tube was not complete. In the most peripheral part of the former tube and in the distal nerve segment great numbers of fine-beaded regenerating fibers were present; hence, much more complete regeneration might have occurred had the period been longer. The architecture of the new nerve differed from the normal in that perineurium and endoneurium were as yet undefined except for some superficial condensation of fibrous layers in the most proximal portion (fig. 8 *B*). In preparations stained with phosphotungstic acid hematoxylin the new nerve throughout its length showed collagen in the

---

EXPLANATION OF FIGURE 8

Fig. 8.—*A*, proximal stump of ulnar nerve, ninety-nine days after subperineurial excision. The original stump lies near the left border, where several Perroncito spirals are seen as dark bodies among the axis-cylinders. The new nerve passes to the right. Gros-Bielschowsky method; cresyl violet stain.

B, cellular detail of the newly formed nerve 3 cm. distal to the point at which *A* was taken.

C, higher magnification of field in *A*, showing axis-cylinders to the extreme right of *A*.

D, distal stump, showing the distal cell mass cut somewhat obliquely. Gros-Bielschowsky and cresyl violet stain.
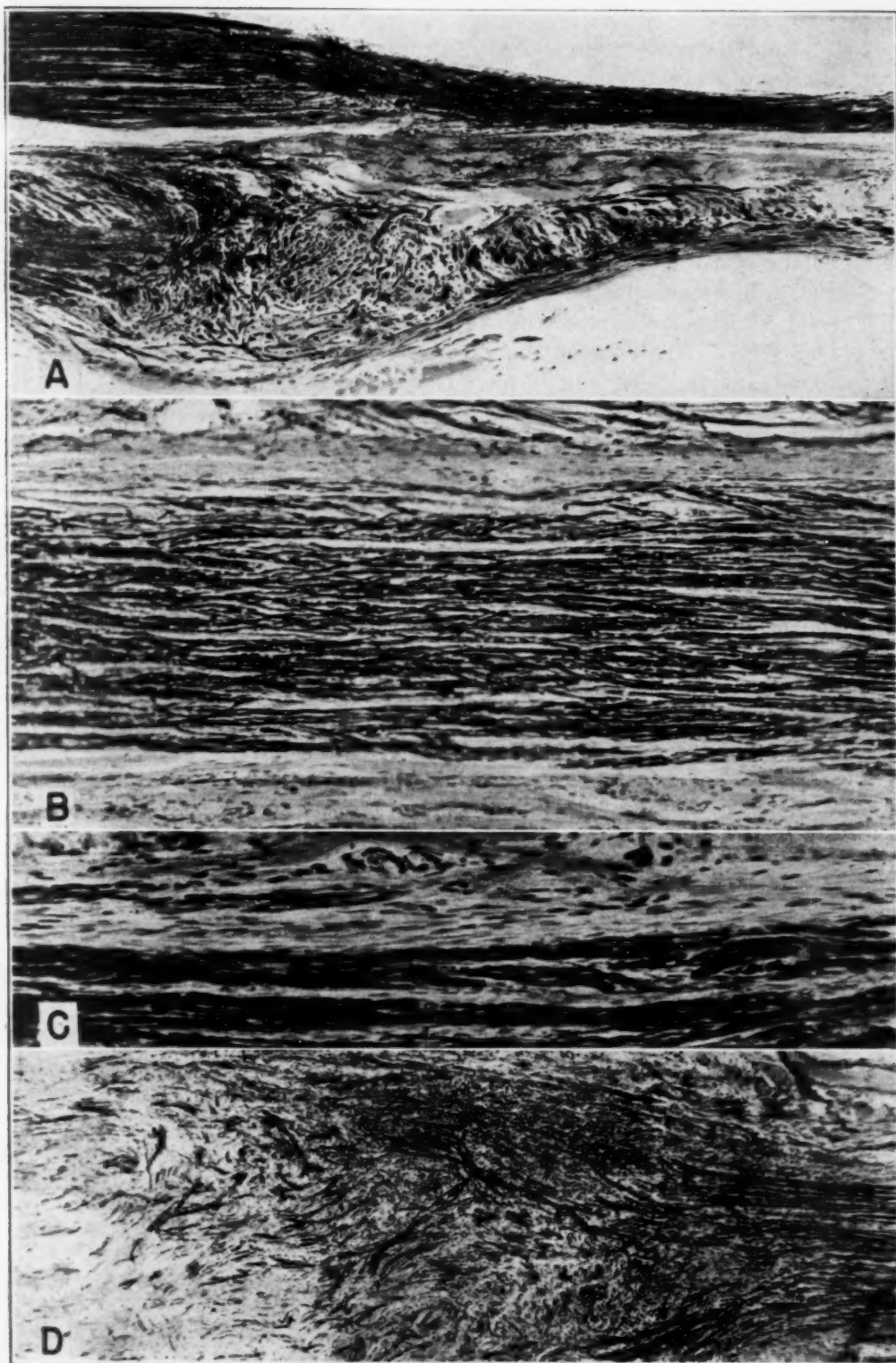
(See legend on opposite page)

form of fine longitudinal bundles. All the nerve fibers had scattered Schwann cells, but the main bulk of the cellular columns was made up of the pale oval fibroblastic cell of endoneurial or perineurial type (fig. 8 B).

SUBPERINEURIAL EXCISIONS OF PERONEAL NERVE

In 3 other long term experiments, the sciatic nerve was exposed at operation and the popliteal division excised for varying distances. The peroneal division was then treated, as was the ulnar nerve in the first experiments. Thus, in the same wound, subperineurial excision of peroneal nerve was tested against total excision of popliteal nerve. The epineurium and the perineurial tube of the peroneal nerve prevented further separation of the two ends of the popliteal nerve.

In such an experiment, 3.4 cm. of popliteal nerve was excised completely, and 3.2 cm. of peroneal nerve was pulled from two openings in its sheath, leaving a gap of 3.2 cm. between the ends. Recovery of some dorsiflexion of the foot was observed clinically on the ninety-third day. Exploration on the one hundred and sixth day revealed that electrical stimulation of the peroneal nerve above the lesion elicited an estimated 30 per cent dorsiflexion of the foot and spreading of the toes and that stimulation of the popliteal nerve produced only a faint flicker in the soleus muscle, without movement of the foot. There was no trace of cross connection. A large neuroma densely adherent to surrounding muscle and areolar tissue marked the situation of the former nerve ends, and a new nerve connected these. Transverse section of the nerve halfway between the neuromas showed two types of regeneration—the one in small bundles of nerve fibers lying in the fibrous tissue and the other in one homogeneous bundle, already showing evidence of independent perineurium (fig. 10 A). There was no difference in the average size of fibers between these two groups. Longitudinal section of the proximal neuroma showed that it was almost wholly

---

EXPLANATION OF FIGURE 9

Fig. 9.—*A*, sciatic nerve, with the peroneal nerve above and the popliteal nerve below. Gros-Bielschowsky method; cresyl violet stain. Both views had been resected from the same level one hundred and six days earlier, the peroneal nerve subperineurially and the popliteal nerve entire. New nerve appears above and a neuroma below.

B, higher magnification of the new peroneal nerve taken just distal to the right of *A*.

C, section similar to *B*, showing condensation of pale nuclei at the edge of the nerve.

· *D*, distal stump of peroneal nerve shown in *A*, showing junction of fibers through the distal cell mass, the diameter of which is about 50 per cent greater than the full diameter of the peroneal trunk, shown here. Section at a superficial level.
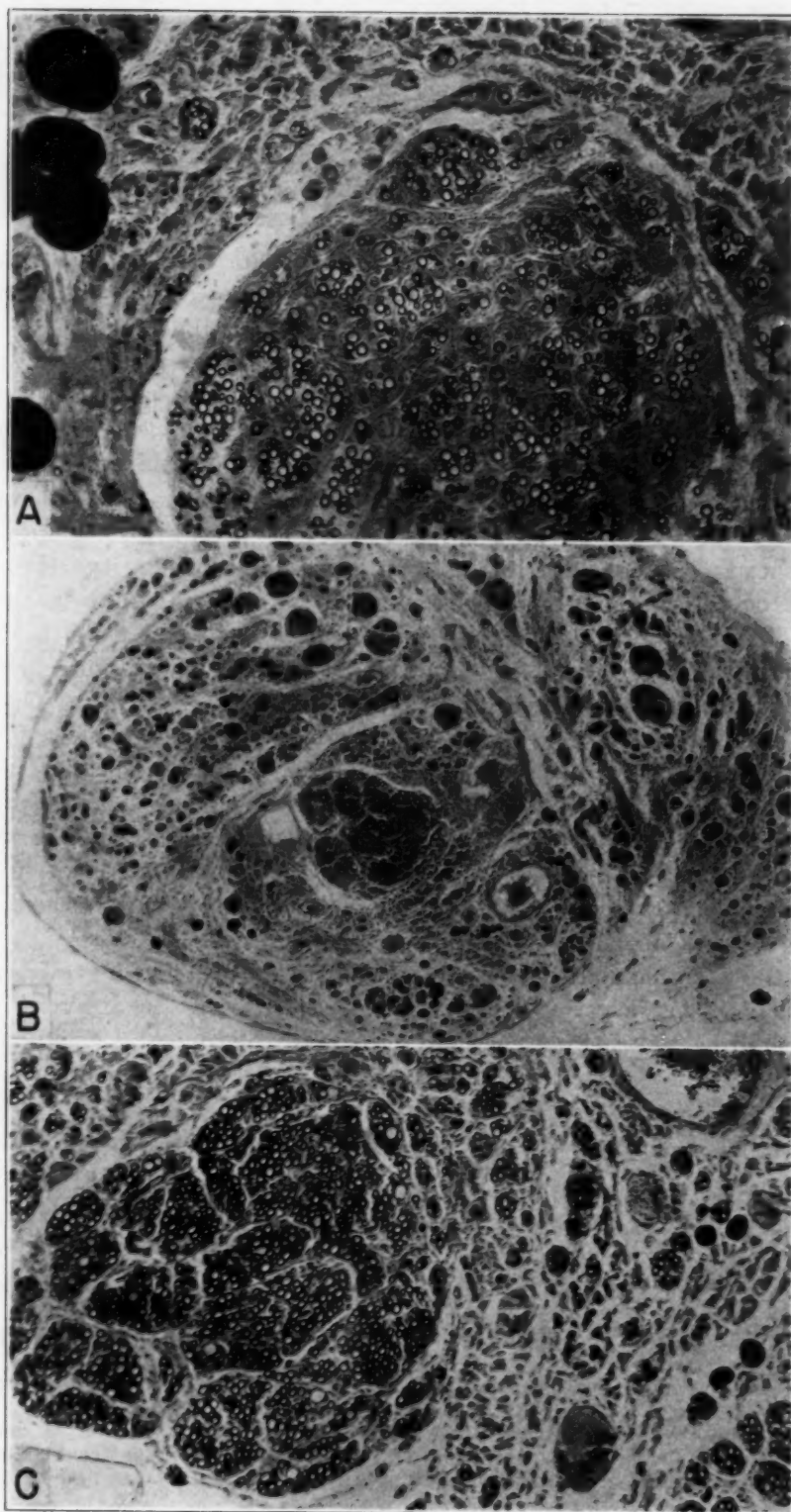
(See legend on opposite page)

composed of a terminal neuroma on the popliteal division (fig. 9 *A*), from which the small separate fiber bundles in the epineurium were derived. The peroneal nerve had reproduced a nerve slightly less than its own diameter, and this was traced directly to the peripheral peroneal nerve trunk, into which large numbers of fibers were entering (fig. 9 *D*). In spite of the absence of any well defined sheath, the straying bundles from the popliteal nerve were not observed to enter the sheath of the peroneal nerve at any part of its course, nor did any of the latter stray into the former group. The new peroneal nerve is shown in figure 9 *B*. It traveled as a compact single bundle for 2.3 cm. and thereafter showed several collagenous subdivisions. At its margin a condensation of flat, pale fibroblastic nuclei represented the new perineurium (fig. 9 *C*). The bundle contained more collagenous material than normal nerve, and this was arranged in longitudinal strands. The Schwann cells and longitudinal vessels were of normal appearance except that absolute parallelism of fibers was not attained.

There were no spirals or reverse turns. The cellular growth from the distal peroneal stump tapered 5.5 mm. proximally, where it merged imperceptibly with the cellular cone of the "tube." There was a slight bulge just proximal to the distal level of section, and here the nerve fibers became tortuous in their course through the cell mass. There did not appear to be any loss of fibers, however, and the peripheral nerve was well filled (fig. 9 *D*).

In a second experiment, the time interval allowed (eighty-eight days) was too short to permit return of conduction across the gaps (4.5 cm.) of either the peroneal or the popliteal division of the nerve. Sections, however, revealed a situation identical with that described in the preceding paragraph. The peroneal bundle traveled as a large single band (fig. 10 *B* and *C*), surrounded by small bundles of popliteal fibers, which frequently turned back. Fibrils had reached the peripheral peroneal stump in large numbers, but few had matured at this level. There was no formation of neuroma at either end, though such masses were prominent in the popliteal division. No exchange of fibers had taken place. In another experiment, in which there were 4.3 cm.

EXPLANATION OF FIGURE 10

Fig. 10.—*A*, transverse section of the new peroneal nerve shown in figure 9 *B*, halfway between the two stumps. Note the stray bundles of popliteal nerve in the epineurium. Osmic acid stain.

B, transverse section of the whole sciatic nerve halfway between the two stumps after total excision of the popliteal nerve, and subperineurial resection of the peroneal nerve ninety-six days earlier. Osmic acid stain.

C, higher magnification of the new peroneal nerve shown in the center of *B*.

of total excision of the popliteal nerve and 5.2 cm. of subperineurial excision of the peroneal nerve and the animal was killed at the end of ninety-six days, faint contraction occurred in the soleus group on stimulation of popliteal nerve above the lesion and no response was elicited from the peroneal nerve. Sections showed a few fibrils entering the peripheral peroneal stump, having just traversed the distal perineurial and endoneurial proliferation, which had formed a moderate distal enlargement. In this case, however, a neuroma had formed at the middle of the gap, and this was found to be due to the rupture and coiling of a nerve branch, which had thus channeled most of the peroneal fibers into a cul-de-sac. Evidently, the initial extraction of nerve contents had taken the perineurium, as well as the nerve bundle, from the lower slit and only the nerve bundle from the upper. Examination of a section of the pulled nerve indicated that only one layer of perineurium was attached to it, but care had not been taken to section either end of the pulled piece.

It is to be concluded, therefore, that excision of a nerve trunk within its perineurium is followed by regeneration of the nerve bundle until functional connection with the distal segment is reached. The nerve was reconstituted over a 3 cm. gap, with a 30 to 50 per cent return of function after approximately one hundred days and with fiber continuity beginning to be established over 4.5 and 5.2 cm. gaps in eighty-eight and ninety-six days, respectively. The control experiments indicate that nerve fibers growing freely across total excisions of nerve, with such framework as the epineurium of a neighboring bundle can provide, can establish contact with the peripheral segment at a similar rate but with such a degree of fiber loss by dispersion that resulting recovery of function is greatly impaired in the larger gaps. Longitudinal section of the epineurium gave frequent evidence of reversal of direction of such fibers growing in simple fibrous tissue.

The presence of a perineurial sheath prevented the formation of both central and peripheral neuromas. A slight swelling of the proximal segment in the early stages represented a coiling of the growing nerve fibers and Schwann sheaths behind the expanding wedge of proximal stump. This phenomenon, with its enclosed Perroncito spirals, later tended to disappear. The perineurial meshwork formed by the collapse of the original perineurial tube was slowly reformed into a laminated sheath for the growing nerve, which eventually establishes contact with the peripheral segment. The latter contributed to the process only by the formation of a conical cellular mass which received and transmitted the nerve fibers that reached it. The central stump provided the reformed nerve with endoneurium and vessels. Some small vessels entered from the walls of the original tube. There appears to be no

limit to the size of the reformed nerve, for the perineurium is expanded by its contents and excites no external fibrosis or adhesions and the prevailing pattern of fibrous tissue is longitudinal rather than transverse.

In this process of reformation of nerve the growing nerve fibers brought Schwann cells with them. The ultimate growing tips of the fibers appeared as chains of beads connected by extremely fine threads. These lay on the surface of the fibroblast cells, being always separated from the nucleus by a space (fig. 15 C), as maintained by Cajal. The growing tip of the nerve fiber was seen as the last of a series of very fine beads connected by a faint thread. No accumulation of Schwann nuclei was found at any one point, and their distribution was sparse, though fairly even throughout the bundles of growing fibers except in the first millimeter of growth and distal to that point. On all fibers which could be traced any distance from the growing tip, the first Schwann cell was encountered about 0.25 mm. proximal from the tip. Mitosis of the last nucleus was not seen in these specimens, though it was frequent in the general region of growth of nerve fibers.

This relationship to Schwann nuclei also held for the fibers growing freely in epineurium, where fibroblastic nuclei of endoneurial type also closely followed the growing fiber, always following the Schwann nucleus and enveloping the fiber (fig. 15 C). In the perineurial tube the growing fiber, likewise, was soon surrounded by a small tube of endoneurial nuclei, characteristic of the smaller fibroblast lying free in fibroblastic network (fig. 15 A and B). These nuclei were then found nearer the growing tip than the first Schwann nucleus. The distinct space between the oval fibroblastic nucleus and the nerve fiber also distinguished these embracing cells. The maturation of an endoneurial sheath of the nerve fiber, including the development of myelin, was equally far advanced at the same level of nerve, whether the nerve fibers were lying within the former perineurial tube or were free in the epineurium.

GRAFTS OF PERINEURIAL TUBE

The possibility that the residual tube of perineurium, surrounded by epineurium, could be utilized to bridge a preformed gap between nerve ends by grafting was explored. For this purpose, both the right and the left ulnar nerve in the upper forelimb of the cat were exposed at operation. The right ulnar nerve was pulled out of its sheaths for a distance by the technic shown in figure 4. A corresponding length of left ulnar nerve was excised completely. The perineurial tube on the right side was cut where it joined the intact nerve at each end. The piece of tube thus excised was then sutured into the gap on the left side, and the piece of entire nerve from that side was sutured into the gap on the right side. The suture was made with fine silk in some

experiments and with fine nylon in others. Each junction consisted
of two sutures, one on each side of the nerve sheaths, holding the
opening of the graft against the cut edge of the nerve. No attempt
was made to protect the suture line.

The elastic tube of perineurium was found to be easy to handle in
this way. As will appear later, the greatest difficulty is in insuring that
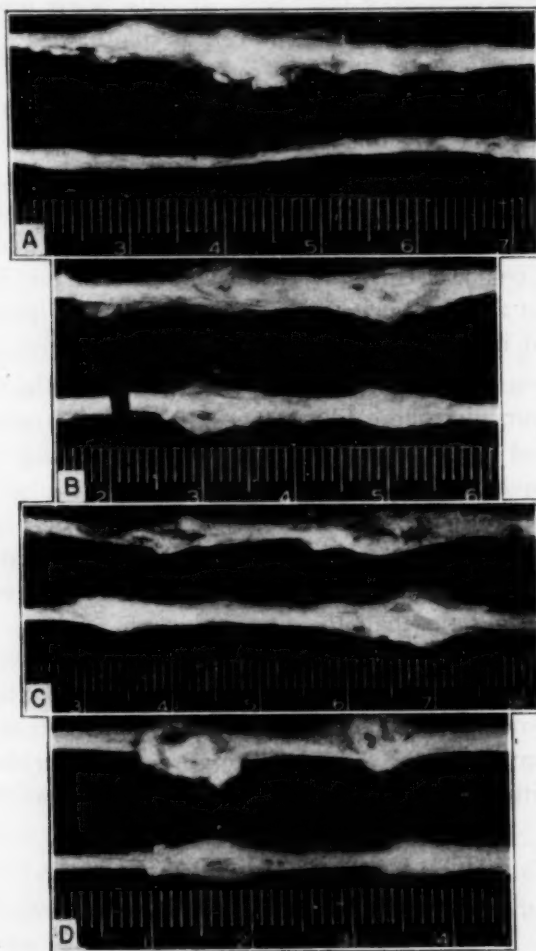
Fig. 11.—Ulnar nerves. (*A*) The left nerve (above) was sectioned in three
places; the right nerve (below) was excised for 3 cm. subperineurially ninety-nine
days earlier. The scale is in millimeters.

B, the left nerve (above) was excised for 2.2 cm. and replaced with whole
graft (frozen); the right nerve (below) was excised for 2.2 cm. and replaced
with graft of perineurial tube (frozen) thirty-three days earlier.

C, the left nerve (above) was excised for 3 cm. and replaced with right ulnar
nerve; the right nerve (below) was excised for 3 cm. and replaced with perineurial
tube from the left ulnar nerve seventy-nine days earlier.

D, the left nerve (above) was excised for 2 cm. and replaced with graft of
whole nerve (frozen) from the other side. The right nerve (below) was excised
for 2 cm. and replaced with graft of epineurium alone (frozen) from the other side
seventy-five days earlier.

the perineurium indeed remains, and section of the piece of nerve originally pulled from the tube was found to be the only way in which the procedure could be adequately controlled. If a transverse section showed more than two lamellas of perineurium adherent to the pulled fragment, it is likely that little remained in the graft.

In such an experiment a gap of 2.2 cm. of ulnar nerve was grafted on each side, and the nerves were explored on the thirty-third day, when the animal was killed. In this instance both the perineurial tube and the piece of intact nerve were frozen hard with solid carbon dioxide for five minutes and then thawed to room temperature before being sutured into position, a procedure designed to test the resistance of the grafts to preservation in vitro. At the final exploration stimulation of the ulnar nerve proximal to the graft was without effect on either side. A swelling had formed at each suture line on each side' (fig. 11 *B*), and the swellings were adherent to surrounding tissue. The whole graft was swollen and adherent, whereas the perineurial graft was chiefly smooth and free from adhesions. The perineurial tube had filled out, and sections showed it filled with fine nerve fibers, oval perineurial cells (fig. 12 *A* and *B*) and small numbers of Schwann cells except at the distal extremity, where the nerve fibrils were finer and the Schwann cells few. The condition was entirely comparable to that of simple subperineurial excision of the ulnar nerve at ninety-nine days described earlier, except that maturation of the myelin sheaths had not occurred and few axons had reached the peripheral nerve.

Large numbers of nerve fibers had likewise entered the autogenous frozen graft of whole nerve on the other side. Few fibers coursed down the center of the graft, where the intercolumnar spaces were unduly wide and more tightly filled with macrophages than in simple degenerating nerve. Except at either end, the Schwann nuclei and Schwann bands of this graft stained more darkly with hematoxylin and eosin than did the normal nerve, whether they had received a regenerating fiber or not. The few Schwann nuclei accompanying nerve fibers entering and leaving the graft for 3 mm. at each end were wider and shorter than the large numbers in the remainder of the graft. The Schwann nuclei directly associated with the axis-cylinder in the middle of the graft appeared not to differ in any way from those remaining unutilized in this region. No necrosis was seen, but the perivascular spaces were greatly widened and the vessels dilated. The number of fibers successfully transmitted to the peripheral trunk by the whole graft and the number transmitted by the perineurial tube graft were approximately equal.

It was found that a small fragment of the original nerve 3.75 mm. in length had been left in the lumen of the perineurial tube and had become encysted by the pale oval endoneurial cells (fig. 12 *B*). Though
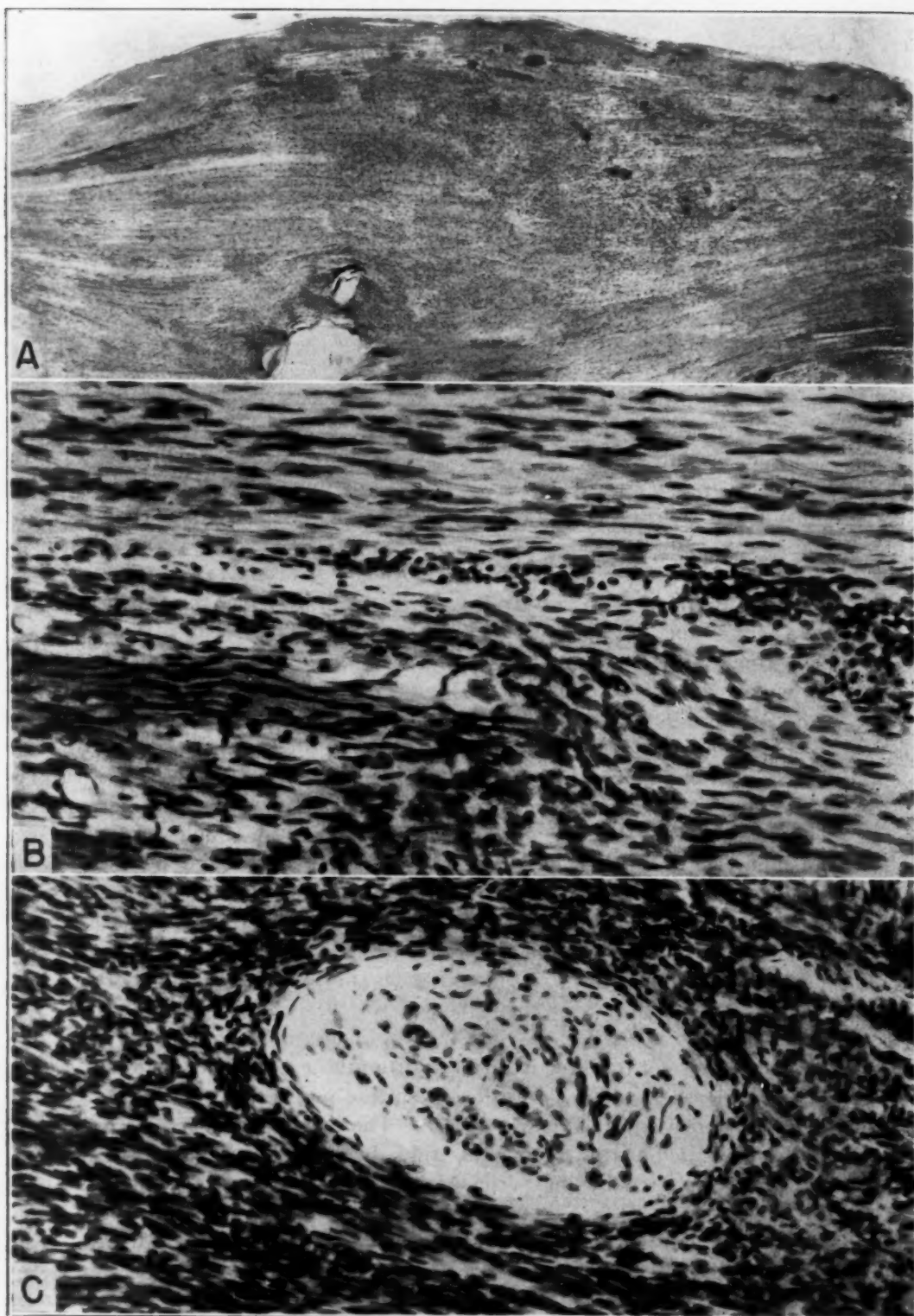
(See legend on opposite page)

phagocytes had engulfed the myelin in these fragments, the Schwann cells stained darkly precisely as did those of the whole nerve graft in the other limb. Further, there was no evidence of division of these encysted Schwann cells or of their contribution to the cell columns (fig. 12 B). The cells lining the cyst were the flat perineurial cells with a large pale nucleus. This observation, and another from a different experiment (figs. 12 C and 15 D), appear to offer further strong evidence against participation of Schwann tissue in regeneration as a primary event.

The graft of whole nerve stained uniformly more densely for collagen than did normal nerve, whereas the perineurial graft showed longitudinal streaks of collagen beginning at the suture line and running throughout its length. Mallory's phosphotungstic acid hematoxylin stain showed the Schwann nuclei as dark blue throughout the two grafts. Those in the perineurial graft were sparsely distributed among the fibroblastic nuclei of the cells columns (fig. 15 D), becoming rarer as the distal end of the graft was reached. They clearly lay in the bundles of nerve fibers and distant from collagen (fig. 15 D). The Schwann nuclei of the graft of whole nerve were evenly and intensely stained throughout except for 3 mm. at either end, where they had been replaced by a few thicker Schwann nuclei of the type found in the scars and directly related to regenerating nerve fibers. These appeared to be migrating nuclei.

The surface of the perineurial graft was identical with normal epineurium and contained numbers of arterioles and venules which had connections with longitudinal vessels but not with surrounding tissue. From the inner aspect of the epineurium fine fibrous overlapping bands, covered with pale oval nuclei, stretched medially and distally to the regenerated nerve bundle as though expanded laterally and distally. These appeared to be the lamellas of a new perineurium, as observed in the experiments on simple avulsion.

In a second experiment, 3 cm. of ulnar nerve was grafted on each side, with the same technic and the animal allowed to survive seventy-nine days. The grafts were permitted to cool to room temperature in saline solution before being sutured but were not otherwise treated.

EXPLANATION OF FIGURE 12

Fig. 12.—*A*, section of proximal stump of the ulnar nerve grafted to perineurial tube (frozen) thirty-three days earlier; cresyl violet stain.

B, section showing the distal end of a fragment of nerve found among the fibroblastic cells almost halfway between the two stumps in the experiment from which *A* was taken. Hematoxylin-eosin stain.

C, a similar fragment lying transversely in another experiment taken seventy-nine days after excision of the main nerve mass.
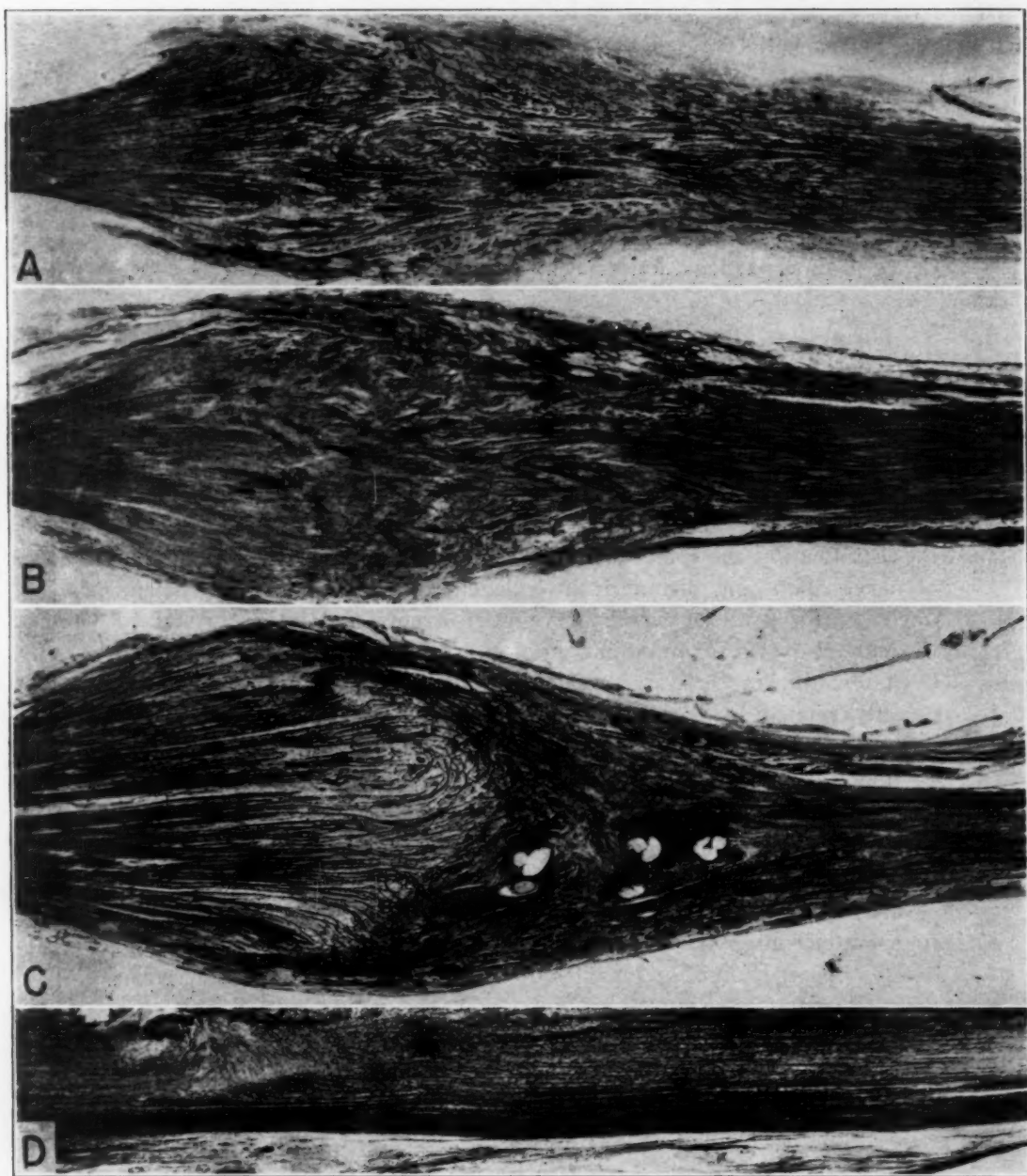
Fig. 13.—A, proximal stump of the ulnar nerve seventy-nine days after graft of the perineurial tube from the opposite ulnar nerve. Gros-Bielschowsky method; counterstained with cresyl violet.

B, section near that shown in A, stained with phosphotungstic acid hematoxylin to show bands of collagen.

C, proximal stump of the ulnar nerve seventy-five days after graft of epineurium from the opposite ulnar nerve. Gros-Bielschowsky method; counterstained with hematoxylin and eosin.

D, proximal stump of the ulnar nerve seventy-nine days after suture to the whole nerve graft. The portion of the swelling containing a suture is not shown. Gros-Bielschowsky method; cresyl violet counterstain.

Fig. 14.—Cross sections of ulnar nerve; osmic acid stain. *A*, middle of perineurial graft after seventy-nine days; *B*, normal nerve at the same level; *C*, middle of epineurial graft (frozen) after seventy-five days; *D*, middle of graft of whole nerve after seventy-nine days; *E*, high magnification of the center of *A*, but counterstained with eosin; *F*, higher magnification of the edge of *A*.

(See legend on opposite page)

On the seventy-ninth day the ulnar nerves were cut proximal to the grafts and stimulated. On the side of the perineurial tube graft a moderate flexion (50 per cent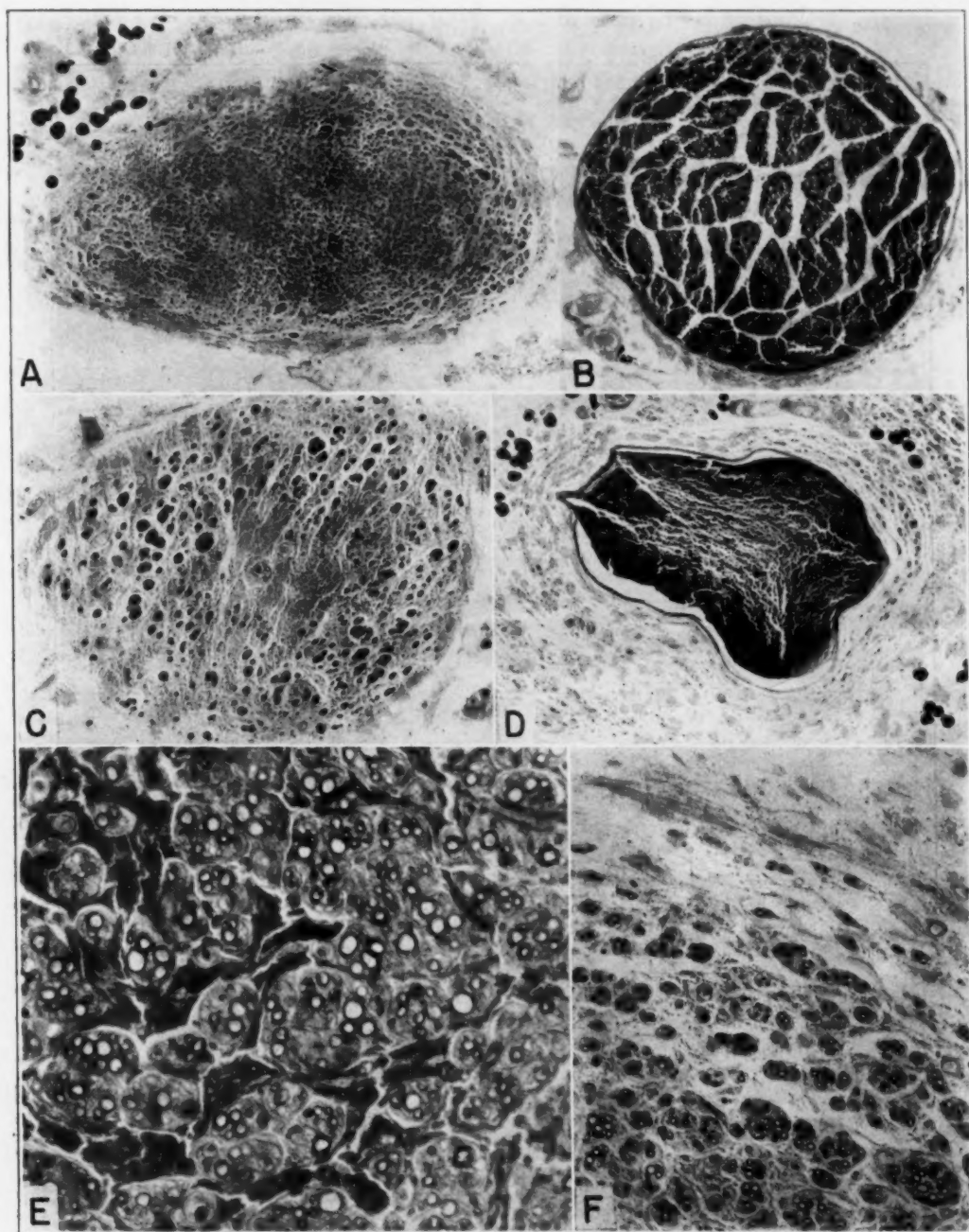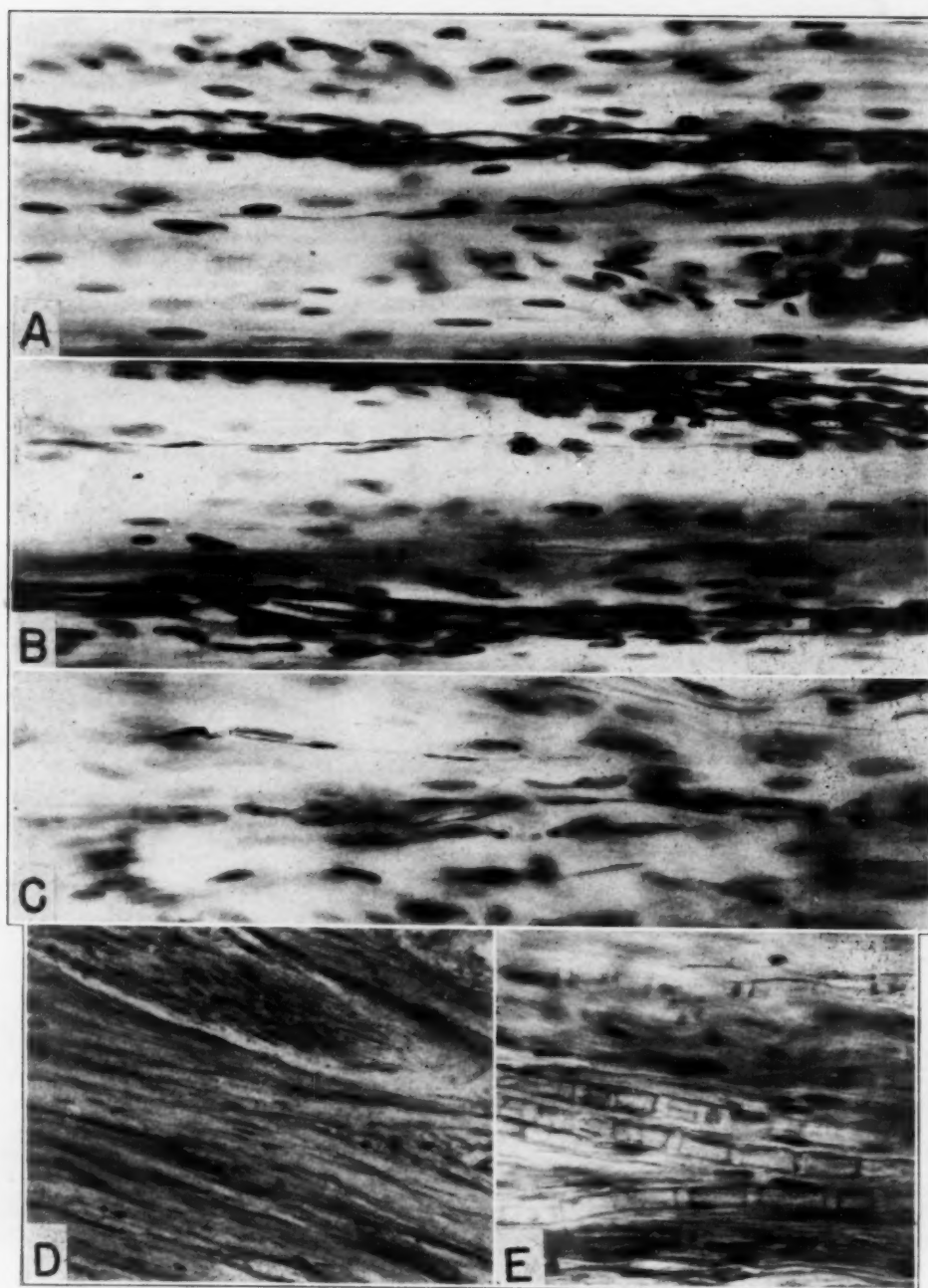) of the wrist and a strong flexion (80 per cent) of digits and protrusion of the ulnar claw were produced. On the side of the whole nerve graft feeble flexion (10 per cent) of the wrist and slight movement of the claw without flexion of digits occurred. Both nerves showed swellings at the suture lines (fig. 11 C), but while the right nerve (perineurial tube) had only a few filmy adhesions to muscle, the left (whole) nerve was densely adherent to all surrounding tissues and was very vascular. The perineurial tube had filled out to the diameter of the parent nerve. On transverse section it presented a diffuse field of medullated nerve fibers with sparse longitudinal endoneurim and beginning perineurium (fig. 14 A, E and F). Longitudinal section showed full regeneration throughout the nerve, with good connection with the peripheral nerve (fig. 13 A). There was no evidence of Perroncito spirals or reversal of direction, and medullation in the peripheral nerve was well balanced. Collagen was distributed in longitudinal bands (fig. 13 B).

The autogenous graft of whole nerve had remained in good apposition to the nerve ends and was conducting fibers with approximately the same stage of medullation at every level as the fibers of the perineurial graft. The nerve fibers, however, mainly lay at the edge of the graft, where they were tightly packed (figs. 13 D, 14 D and 16 D). The Schwann nuclei showed the same peculiarity of dark staining noted in other grafts of whole nerve. In this graft central necrosis had occurred at two levels. In each case the Schwann nuclei had disappeared, and

---

EXPLANATION OF FIGURE 15

Fig. 15.—A, distal end of ulnar nerve of a seventy-nine day perineurial graft. A bundle of nerve fibers with condensation of the endoneurial sheath and fibroblastic nuclei is shown above. A regenerating single fiber runs across the middle of the figure. At the center is a Schwann nucleus closely applied to the axiscylinder, the last nucleus before its growing tip, which was 0.25 mm. away to the right of the figure. The long oval nuclei below accompany a strand of collagen. Gros-Bielschowsky method, hematoxylin-eosin counterstain.

B, section similar to that in A, showing another terminal Schwann nucleus.

C, regenerating filaments of popliteal nerve in the epineurium of the remaining peroneal nerve, eighty-eight days after excision, showing a terminal Schwann nucleus on a fiber growing between epineurial fibroblasts. Note the absence of endoneurial fibroblasts around the fibril at this stage, though they accompany the bundle of fibrils below.

D, section of the ulnar nerve, showing contents of perineurial tube stained with phosphotungstic acid hematoxylin (Peers's modification). An encysted fragment of the avulsed nerve lies above. Of the cellular contents of the remainder of the tube (compare figure 12 B) only strands of collagen and a few rod-shaped Schwann nuclei in the interspaces and in the encysted fragment are stained here.

E, channel between strands of collagen in regenerating peroneal nerve one hundred and six days after subperineurial avulsion, showing Schwann nuclei at the edge of developing myelin sheaths. Same stain as that employed in D.
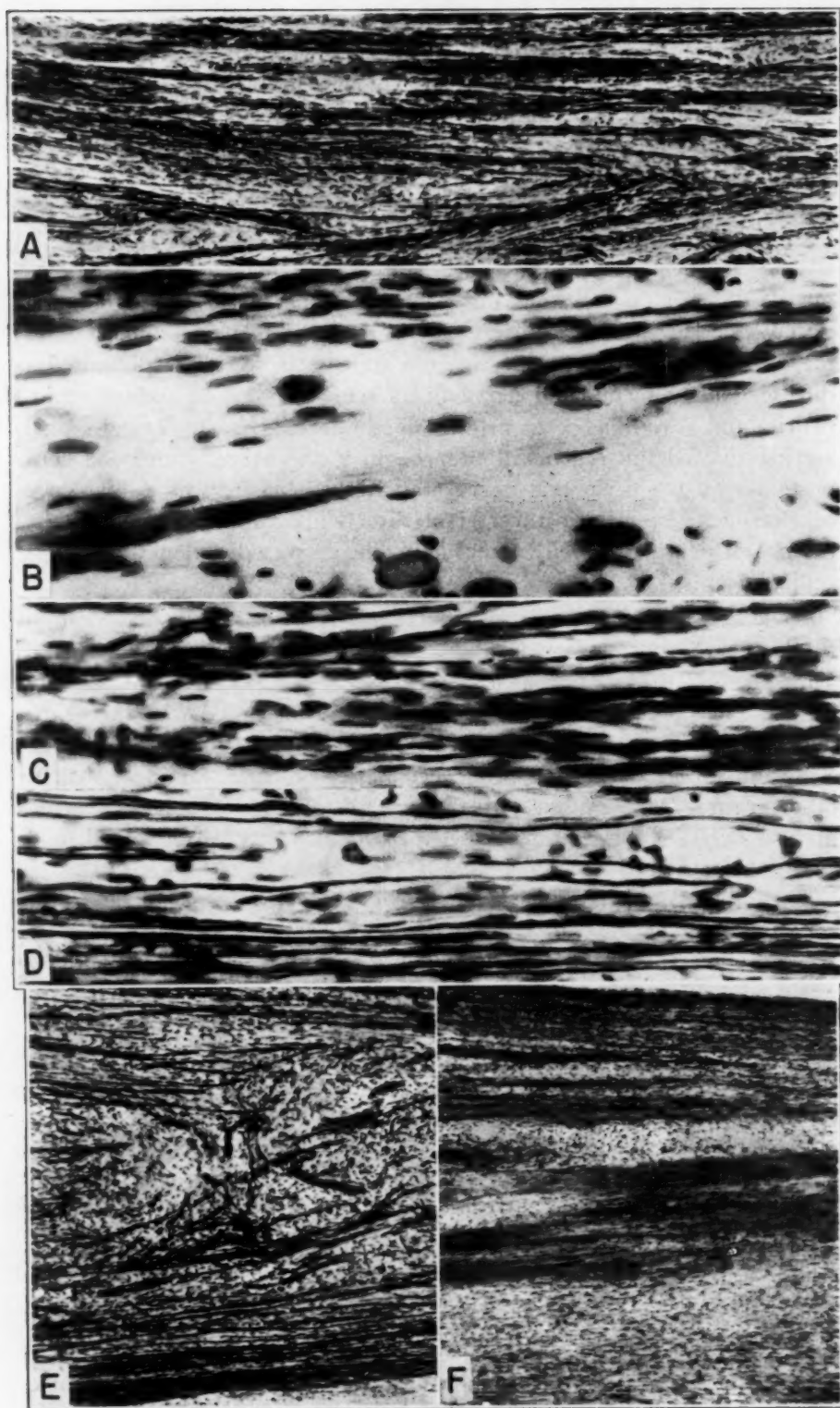
(See legend on opposite page)

in 1 instance there was some cavitation, in which nerve fibers coursed irregularly and lost direction (fig. 16 E). Dense collagen had been deposited in these areas (fig. 16 F), and slighter collagenization was present throughout.

One further experiment deserves mention on account of an instructive mishap. Two centimeters of ulnar nerve was grafted on each side, as in the preceding experiments. Both the perineurial graft and the whole nerve graft were frozen in solid carbon dioxide for five minutes and thawed to room temperature before suture. Unfortunately, it was later found that the perineurium had been pulled with the nerve contents, leaving only epineurium. The experiment, however, serves as a control of those already reported. The animal was killed at the end of seventy-five days, at which time it was found that both nerves conducted motor power well, that of the short epineurial graft almost perfectly (95 per cent) and that of the whole graft moderately well (50 per cent). The epineurial graft was slender, smooth and not adherent to any structure (fig. 11 D). The whole nerve graft was bound down to all tissues with dense and very vascular adhesions. Transverse section of the epineurial graft (fig. 14 C) showed that the regenerated medullated fibers lay in small discrete bundles in heavy fibrous tissue. The most striking feature of the epineurial graft was the lack of mass invasion of fibroblastic tissue at the proximal suture line (fig. 13 C). The experiment indicates the possibility of conduction of growing nerve fibers by simple fibrous tissue, provided the distance is short and the direction of fibers purely longitudinal, as in epineurium. Close inspection revealed that fibers were frequently lost by reversal of direction, but as the distance was very short in this experiment it mattered little. Endoneurial tissue invaded the fibrous mesh with the Schwann cells, which followed the

EXPLANATION OF FIGURE 16

Fig. 16.—A, longitudinal section of the nerve developed within the grafted perineurial tube seen in transverse section in figure 14 A. Gros-Bielschowsky method; counterstained with cresyl violet.

B, border of the same nerve as that shown in A, under higher magnification, showing oblique sheets of collagen with large flat cells passing from the epineurium, below (vessels in section), to the border of the nerve, above.

C, higher magnification of the axis-cylinders shown in A, revealing beaded appearance tyical of recently regenerated fibers.

D, section near the edge of an autogenous graft of the ulnar nerve seventy-nine days after operation, showing the irregular caliber of the axons and their close adherence to the rodlike Schwann cells of the graft. Numerous phagocytes remain. Gros-Bielschowsky method; cresyl violet stain.

E, section lower in the same graft as that from which D was taken, showing distortion and reversal of nerve fibers as they reach an area of central necrosis.

F, section from the same graft, showing dense collagenization of the central necrotic area, with diffuse light deposit in the rest. Hematoxylin stain. The stained nuclei include those of the Schwann cells (dark rods) and those of phagocytes and, very lightly stained, those of endoneurial fibroblasts.

nerve fibers to build in miniature the architecture for each small nerve bundle. The graft of whole nerve on the opposite side of this animal showed the characteristics described for earlier experiments, including central necrosis.

COMMENT

The differences between the cellular structure of the perineurium and that of the endoneurium are quantitative rather than qualitative. Each contains, besides wandering histiocytes, two types of mesoblastic cells. One of theses is a fibroblast, which is profoundly stimulated by nerve injury. That proliferation of the endoneurium provided a framework for the regeneration of nerve across gaps in its continuity was advocated by Hjelt [34] in his early experiments on frog nerves, in 1860. Hassin [2] has more recently returned to this view and asserted that after degeneration of the nerve fibers most, if not all, Schwann cells of the peripheral nerve are converted to phagocytes and lost. Although we do not subscribe to this view regarding the fate of the Schwann cells, the cells in the immediate vicinity of the cut ends are certainly lost. The experiments cited in this paper offer evidence that the junctional tissue is provided by the fibroblasts of the endoneurium and the perineurium. The view that such tissue results from proliferation of Schwann cells is disproved by the consistent staining of the nuclei of these cells with the phosphotungstic acid hematoxylin method and the proof of the relationship of these cells to axis-cylinders in alternate sections of material embedded in pyroxylin and stained with this method and with the Gros-Bielschowsky technic. By the facility thus gained, the migration of such nuclei was traced after the invasion of nerve fibers. Such a migration is fully consistent with the observations of Speidel [35] on amphibians. The perineural lamellas are lined with large flat cells with a pale oval, or nearly circular, nucleus, larger than the fibroblast. These cells are also found. in the endoneurium ("fixed connective tissue cells," Doinikow [31]) near blood vessels. They are carried into a neural scar by the fibroblastic proliferation but retain their staining characteristics. In inflammatory conditions we have seen them give rise to the macrophage. In appearance and behavior they closely resemble the mesothelium of peritoneum or pleura. More investigation is necessary before the character of these cells can be finally settled. Perineurium and endoneurium therefore normally differ only in the

34. Hjelt, O.: Ueber die Regeneration der Nerven, Virchows Arch. f. path. Anat. **19**:352-367, 1860.

35. Speidel, C. C.: Studies of Living Nerves: I. The Movements of Individual Sheath Cells and Nerve Sprouts Correlated with the Process of Myelin Sheath Formation in Amphibian Larvae, J. Exper. Zool. **61**:279-331, 1932; IV. Growth, Regeneration, and Myelination of Peripheral Nerves in Salamanders, Biol. Bull. **68**:140-161, 1935.

proportion of content of these two cell types. The endoneurial and perineurial fibroblast appear to be identical, and we suggest that they together be called "neural fibroblasts." The neural fibroblast differs from the epineurial fibroblast in its staining properties and the type of collagen deposited.

The regenerating nerve fiber is certainly free from any sheath for the first 0.25 mm. unless Schwann cells are already provided, as in the distal nerve trunk. It is therefore not necessary for Schwann cells to be provided for the regeneration of the nerve fiber. The natural cement substance of divided nerves, the neural fibroblastic tissue, tends to lateral diffusion and the production of shapeless masses when left to sprout uncontrolled. The mesothelium which normally limits it is drawn into a mixture from which it cannot reform a membrane, except around individual nerve fibers.

In epineurium the nerve fiber was found to be regularly accompanied with two distinct types of cells to within 0.25 mm. of its growing tip. One of these was the elongated nucleus of Schwann, closely applied to the fibril, which was thickened at or just beyond the Schwann nucleus. The other, which always lay separated from the fibril by a space was a cell with oval, pale nucleus, often curved so as partly to embrace the fibril in its concavity. This inner sheath cell appeared to be the neural fibroblast, though the large perineurial cells commonly formed a further covering.

A tube of perineurium, formed by extraction of the contained nerve bundle, condenses to form a column of fibroblastic cells, the core of which differs considerably in appearance from that of simple fibrous tissue or epineurium but is identical with the neural fibroblast, whose proliferation from the nerve stumps contributes further cells at each end. The specialized cells of this core conduct regenerating nerve fibers without obstruction, and those nearest appear to become immediately oriented to the regenerated fibril so as to enclose it in a tube. From the fibroblastic network the entry of nerve fibers thus produces a multitude of small fibroblastic tubes. Many nerve fibers of later arrival enter tubes already in formation, so that in time each tube contains a group of nerve fibers, one or two of which are more mature than the others. The large flat perineurial cell evidently has a remarkable propensity for encysting Schwann tissue, for instances of envelopment of dead residual fragments of the avulsed nerve bundle were seen. This points to some specific attraction which collects these cells from the mixed matrix.

This process of regeneration of nerve fibers within a preformed perineurial tube differs from growth free in scar in that lateral escape of the nerve fibers is prevented and the loose central network provides a path of least resistance as compared with the fibrous epineurial cov-

ering. Small bundles do undoubtedly escape from the main group, but in the greater resistance of the epineurium they have a greater opportunity of reentry to the core than of defeat or reversal. The main bundle thus formed tends to split into from two to six subsidiary bundles after the first centimeter, but each of these bundles remains large and compact as compared with the many fine bundles which form in epineurial fibrous tissue.

The regenerated nerve within a perineurial tube appears to determine its own diameter according to the number of fibers conducted. Transverse or circular fibrosis was not found, and the longitudinal lacework of the epineurium is not such as to prevent lateral expansion of the contents. On the other hand, the new nerve fibers lack the absolutely parallel course they pursue in a nerve graft or a peripheral degenerated nerve. The zigzag course pursued by each fiber did not affect its rate of growth or of maturation.

The experiments demonstrate, therefore, that regeneration of nerve can occur rapidly and efficiently in a framework provided by the perineurium and that the Schwann sheath can be efficiently and automatically provided for a whole bundle of nerve fibers where none previously existed. The mode of production of Schwann cells in these circumstances is uncertain, but the lack of accumulation of cells at any one point suggests that they are provided by repeated budding of the most distal nuclei.

The interior of the newly formed nerve bundle contains more collagen than does normal nerve, and the presence of broad strands of this substance tends to break up the new nerve into separate bundles after the first 1 to 3 cm. The strands of collagen lie longitudinally, and it would appear that the longer the fibroblastic tissue remains inactive the more such strands are formed. Tension, probably through the more prolonged ischemia thus produced, increases the amount of collagen in perineurial grafts, as in grafts of whole nerve. In the absence of inflammatory reaction, like that which surrounds a ligature which pierces the tube, diffuse collagen formation, such as occurs in grafts, does not occur within the perineurial tube. In the autografts of whole nerve in these experiments there was considerable shrinkage, with the appearance of diffuse collagen. This change was associated with reactive changes in the endoneurial fibroblasts, such as Brenner and I have also noted in ischemia due to pressure [26] and percussion [18] but of greater severity. Such change is held responsible for the uneven caliber of axiscylinders in grafts of whole nerve. The perineurial tube grafts had not undergone this transformation, possibly because no old framework existed for subsequent condensation. A similar change at a longer interval in such grafts is considered unlikely, for robust nerve fibers had already established their own loose collagenous "tubes."

In recording their disappointing experience with homografts, Seddon and Holmes [9] suggested the possibility of a specific tissue immunity as the cause of the complete collagenization in and around the graft, for such an extreme change did not occur in animal experiments. In experiments which my colleagues and I have conducted diffuse collagenization had occurred even in autografts, and we are disposed to regard the process as a result of inflammatory reaction, differing only in degree in different kinds of grafts. The distribution of nerve fibers at the periphery in partly successful grafts indicates that vascular factors enter into the process; but inflammatory reaction is also influenced by these factors, and we are impressed by the frequent narrowing of axis-cylinders in the areas where vascular supply is presumed to have been adequate.

From our experiments we are convinced that no cut nerve end remains of normal structure. Schwann cells are lost for at least 3 mm. and damaged for 1 or 2 cm. Fibroblastic proliferation is inevitable in this region, and usually for a much greater distance. Connective tissue does not invade nerve sutures or grafts; it is there already. The factors which make for collagenization are those that influence the maturation of the endoneurial and perineurial fibroblast. The first of these is the age of the cell, and this must be considered in relation to the opportunity of the cell to undergo specialized development. There is good evidence that the young fibroblast when allowed to redevelop its specialized function as sheath to a nerve fiber will do so to perfection. The older cells lying in clumps appear to become surrounded by collagen, and this thickens into coarse strands as the nuclei assume their resting staining characteristics. The distal fibroblastic mass in a perineurial graft is already more dense after three months, and this process, which manifestly depends on the time elapsed before nerve fibers reach the peripheral end, limits the useful length of the perineurial tube. This possibility did not occur in our experiments, but it could be overcome if necessary by excision and renewal of the peripheral junction. The remaining factors known to affect the development of fibroblasts are tension and ischemia and are probably interrelated. Both should be avoided as completely as possible in all sutures and grafts.

The possible practical utility of perineurial tubes for bridging gaps in human nerves raises two immediate questions: namely, the estimation of the ultimate efficiency of such grafts, and the problem of securing adequate perineurial tube for human nerve.

The question of efficiency of nerve graft can finally be settled only in human experiments, for it has been abundantly demonstrated that the nerves in animals show astonishing power of regeneration through all manner of gaps and obstacles. The crossing of a gap of 3 cm. in a small animal may mean regeneration through half the extent of a limb,

but the factors involved appear to correspond to those active in the same absolute length of gap in man. With this qualification in view, however, one may indicate the salient points of a comparison between a perineurial tube graft and an autogenous whole nerve graft.

My own experiments showed that fresh autogenous nerve graft underwent a tissue reaction which caused shrinkage and collagenization. These grafts, nevertheless, conducted nerve fibers on which myelin matured in a natural manner, but the grouping of fibers at the periphery and the shrinkage indicated that the graft would not transmit the number of fibers it originally contained and the fibers were irregular in caliber. The adherence of epineurium to surrounding structures deprived the nerve of freedom of movement.

The perineurial graft, on the other hand, was not adherent to surrounding tissue except at the suture lines, and these could undoubtedly be perfected by utilization of one or another of the existing intubation technics.[36] The slender structure of the graft enables revascularization to be rapid, and its probable metabolic rate suggests the possibility of survival for a long period by diffusion alone. There appears no reason to make its diameter approximate that of the recipient nerve except so far as its opening may stretch over the nerve end. It is moderately extensible and has no physiologic limit to length. It certainly undergoes fibrous partition after the first 10 mm., but the partition is vertical and does not give evidence of limiting the development of nerve fibers. The resulting nerve bundles are not strictly parallel, but this feature did not in my experiments emerge as of any importance in ultimate conductile efficiency.

The most obvious disadvantages appear in the experiments here recorded. It is difficult to be sure that sufficient lamellated perineurial sheath remains to form a lining to the tube. This can be satisfactorily determined only by transverse section of the nerve substance withdrawn from the tube. The greatest difficulty is in finding a donor nerve with sufficient length within one perineurial compartment. Few nerves travel far within a single perineurial sheath before undergoing fascicular division. A single large trunk in man, such as the posterior tibial nerve, is found on section to consist of seven to ten small fasciculi, each with a separate perineurium. The ulnar nerve, usually a single fasciculus in the cat and monkey from the brachial plexus to just above the elbow, sometimes divides into two or three fasciculi at the midhumeral level in man. More success is likely with selection of one of the largest of the fasciculi of the sciatic nerve, which run distances of many centimeters before regrouping and are clearly visible to the naked eye. The perineurium and epineurium are extremely resistant to cold as com-

36. Weiss, footnotes 4 and 17.

pared with Schwann cells, and it should be possible to use the frozen-dried or a similar technic [37] with success in amputation or autopsy material. For autografts only short lengths of sural nerve appear possible, for this nerve usually runs in two perineurial sheaths for 6 inches (15 cm.) or more. A complete survey of the structure of the perineurial sheath of all cutaneous nerves in man would appear to be desirable if this procedure is considered of practical importance.

The relatively short survival periods employed in the present experiments is due to my assignment to duties overseas. My colleagues and I have carried out a homograft and subperineurial excisions of extreme length (9.5 cm.) in macaque monkeys; but it will be many months before adequate assessment can occur, and the results will be reported at a later time.

CONCLUSIONS

1. The perineurium and endoneurium of peripheral nerve are formed of specialized connective tissue cells of two types. One is a large flat cell of mesothelial type, seen typically in the perineurial lamellas. The other is a specialized fibroblast.

2. The Schwann cells play only a subsidiary part in the regeneration of nerve. The neural fibroblast is immediately activated by injury and then proliferates. It invariably accompanies regenerating nerve fibers, often preceding them, and ensheaths newly formed nerve fibers and bundles. The large flat mesothelial cells provide an outer perineurium.

3. The uncontrolled migration of these mesoblastic cells is responsible for the traumatic neuroma. Dispersal can be prevented by the provision of an intact perineurial sheath.

4. The fibrosis of suture lines and grafts is associated with previous activity of the neural fibroblast. Factors of importance in the production of collagen by these cells when once activated are ischemia, tension and their aging without provision of nerve fibers.

5. The perineurium can be utilized for efficient repair of defects in nerve.

Boston City Hospital.

---

37. Weiss, P., and Taylor, A. G.: Repair of Peripheral Nerves by Grafts of Frozen-Dried Nerves, Proc. Soc. Exper. Biol. & Med. **52**:326-328, 1943; Histo-mechanical Analysis of Nerve Reunion in the Rat After Tubular Splicing, Arch. Surg. **47**:419-447 (Nov.) 1943.

VASOPARALYSIS AND VASOTHROMBOSIS OF THE BRAIN IN INFANCY AND IN EARLY CHILDHOOD

I. MARK SCHEINKER, M.D.

CINCINNATI

THE current teaching of a large number of pathologists in regard to lesions of the central nervous system might be summed up in the doctrine that in the absence of organic disease of blood vessels, such as arteriosclerosis or syphilis, the alterations in nerve tissue must be interpreted as "primary degenerative" or "toxic." The main interest in the vascular lesions of the brain has always been centered on the organic type of arterial disease. Only recently has attention been called to the importance of so-called functional, or reversible, circulatory disturbances, described as "vasoparalysis"[1] and "vasothrombosis."[2] It has been pointed out that a change in caliber of a blood vessel might, under certain circumstances, be as detrimental to the brain tissue as a mechanical obstruction caused by arteriosclerosis. Obviously, mere dilatation of an otherwise normal vessel is not evidence of vascular abnormality. A certain degree of congestion may be physiologic. However, if dilatation and congestion occur in combination with signs of stasis and are associated with increased permeability of the vessel wall for serous fluid and red blood cells, they would appear to be significant in the production of histologic lesions. Such alterations cannot be imitated by postmortem change.

The present report aims to emphasize the significance of functional circulatory disturbances in the central nervous system of infancy and early childhood. The following 3 cases of "encephalitis" illustrate the clinical symptoms and the pathophysiologic mechanism of functional circulatory disturbances in three different phases of development.

REPORT OF CASES

CASE 1.—A 3 year old Negro girl had been well until the day prior to her admission to the hospital, when it was noted that she vomited intermittently

throughout the day, became drowsy and had generalized convulsions. The child had had a normal birth and was normally developed. She was "bright" mentally. The only illnesses had been mumps and measles four months before this admission. In the receiving ward the patient's temperature was 99.4 F. rectally. On reaching the ward, the child was having convulsions, and the temperature was 100.4 F. Fit succeeded fit despite seven intramuscular injections of phenobarbital sodium,

Fig. 1 (case 1).—Coronal sections through both hemispheres, displaying fulness of the white matter and compression of the lateral ventricles.

each of 1 grain (65 mg.). She was in coma between seizures. The attacks lasted from five to ten minutes, beginning in the right or the left side of the face or in the right upper extremity. The deep reflexes could not be obtained. The pupils were fixed to light.

The temperature, which was only slightly elevated on her admission, rose to 103 F. five hours later and to 105 F. seven hours after admission. The pulse

rate rose with the temperature and became irregular; respiration soon became fast and was labored. Periods of apnea were noted twelve hours after entry.

The child never roused from coma and died after thirty-seven hours in the hospital, despite symptomatic supportive therapy.

Laboratory Data.—A single urinalysis revealed sugar and acetone. The white blood cell count was 18,000 leukocytes on two occasions, of which 50 per cent were lymphocytes; the hemoglobin measured 11 Gm. per hundred cubic centimeters; the Kahn reaction of the blood was negative. Determinations of the blood
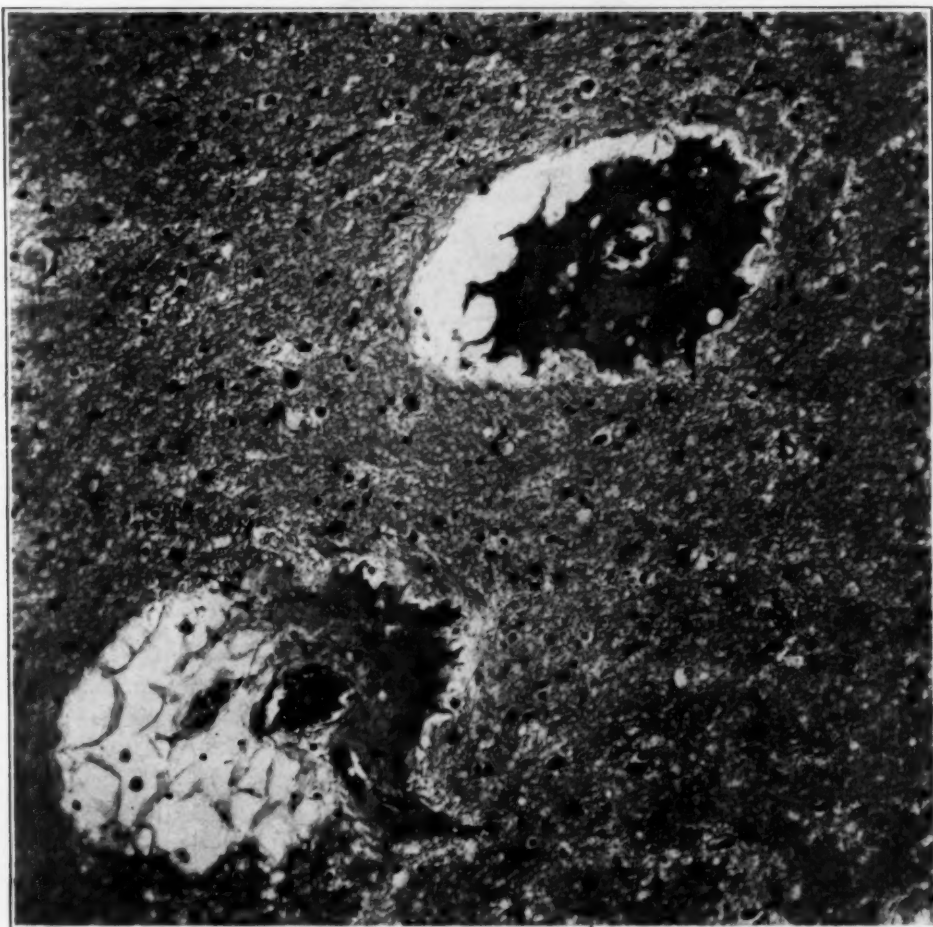
Fig. 2 (case 1).—Tremendous distention of the perivascular spaces with the large masses of transudated serous fluid. Note the absence of edema in the adjacent nerve tissue. Hematoxylin and eosin stain; × 160.

sugar, made on the successive days, were 200 and 153 mg. per hundred cubic centimeters, respectively; the carbon dioxide–combining power on the final day was 34.5 volumes per cent. The blood culture proved sterile.

The first spinal puncture revealed a pressure of 185 mm. of water; and 10 cc. of bloody fluid was obtained, containing 32,000 erythrocytes and 150 white blood cells per cubic millimeter. The tap was repeated ten hours later, when the child

was having labored respiration with periodic apnea. Clear spinal fluid was obtained, under a pressure of 390 mm. of water; the cell count was 250 erythrocytes and 29 white blood cells per cubic millimeter; the protein measured 200 mg., the sugar 132 mg. and the chlorides 774 mg. per hundred cubic centimeters. This specimen of spinal fluid was obtained after the administration of three

Fig. 3 (case 1).—Extremely distended perivascular space, harboring gitter cells. Note the early stage of liquefaction of the surrounding tissue. Hematoxylin and eosin stain; × 220.

infusions of a 5 per cent solution of dextrose, the last having been begun one and a quarter hours before the lumbar puncture.

Autopsy.—The pathologic changes, exclusive of those of the nervous system, were pulmonary edema and cloudy swelling of the cells of the liver, heart and kidneys.

Gross Examination of the Brain: The brain appeared generally full; the gyri were flattened and broadened; the sulci were partially obliterated. There was a slight accumulation of serous fluid about some of the major cerebral veins. The leptomeninges appeared otherwise normal. The under surfaces of the several lobes were not remarkable except for bilateral uncal herniation of moderate degree.

Coronal sections through both hemispheres displayed an obvious fulness of the white matter and compression of the ventricles (fig. 1). There was a slight degree of congestion of the vessels of the centrum semiovale.

Microscopic Examination: Sections were taken from several areas of the gray and the white matter of both hemispheres and from the basal ganglia, medulla and cerebellum. Sections from all these areas were stained with hematoxylin and eosin and cresyl violet, the Loyez stain for myelin sheaths and the Bodian 1 per cent Protargol (strong protein silver) method.

Microscopic examination disclosed the same alterations throughout both hemispheres. The most striking was the tremendous distention of the perivascular spaces (figs. 2 and 3). They harbored large masses of serous fluid and a small number of gitter cells. As a rule the transudation of serous fluid was confined to the Virchow-Robin spaces. Occasionally, however, disruption of the limiting glial membrane had taken place, with escape of serous fluid into adjacent parenchyma. The blood vessels revealed only a slight loss of stainability of their cellular elements. There was no perivascular cuffing. The vascular alterations were noted throughout the subcortical and the central white matter and were seen chiefly in medium-sized and small veins.

Alteration of the nerve parenchyma, secondary to the circulatory disturbances, was perivenous in distribution and was generally seen in the immediate vicinity of the blood vessels. The myelin sheaths showed degenerative alterations in the form of globular swelling, irregular outline or complete loss of stainability. The nerve fibers suffered correspondingly in the same perivascular areas. There was an appreciable reduction in the number of axons; the remaining fibers disclosed degenerative lesions, characterized by swelling, tortuosity and occasional splitting of some of the axons. The glia showed ameboid degeneration and clasmatodendrosis.

The cerebral cortex and the leptomeninges were normal.

CASE 2.—A 5 month old white girl was admitted to the Cincinnati General Hospital on Aug. 12, 1944. She had been irritable, restless and crying for three days and nights. On the evening of August 10 a physician had found the baby normal. On the morning of August 12 there developed irregular, shallow and labored respirations, which led to the child's admission.

On her admission she was in coma and cyanotic; the respiratory rate was about 150 per minute; the pulse rate was 150, and the temperature was 108 F. The extremities were cool, whereas the trunk was hot. The feet were strongly plantar flexed. The examination could not be thorough, since the condition of the child was precarious. She survived less than twelve hours after admission. Therapy included oxygen, intravenous administration of fluids and vigorous efforts to control the hyperpyrexia, the temperature being 107 to 109 F.

Laboratory Data.—The urine was normal. The white blood cell count was 22,400, with a lymphocyte count of 56 per cent. The hemoglobin was 9 Gm. per hundred cubic centimeters. The blood culture was sterile. Culture of stools showed no typhoid or dysentery organisms. The blood carbon dioxide–combining power of the blood was 27 volumes per cent.

Lumbar puncture revealed a normal condition of the spinal fluid.

Autopsy.—The pathologic condition found, exclusive of changes in the nervous system, was bronchopneumonia.

Gross Examination of the Brain: Inspection revealed slight fulness and broadening of both hemispheres. The pertinent gross changes are well illustrated in figure 4. Most of the sections of the brain disclosed numerous disseminated hemorrhages, ranging from the size of a pinpoint to 2 mm. in diameter. They were confined to the subcortical and the central white matter. The cortical gray
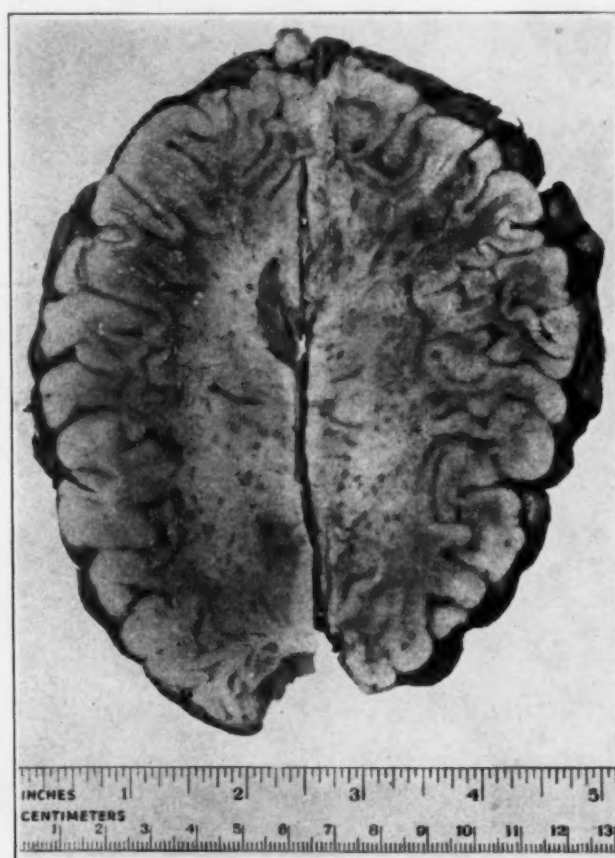
Fig. 4 (case 2).—Horizontal section through both hemispheres, showing a large number of pinpoint hemorrhagic lesions, chiefly confined to the white matter.

matter and the basal ganglia were relatively well preserved. The cerebellum showed marked congestion and a few scattered petechial hemorrhages in the vicinity of the dentate nuclei.

Microscopic Examination: The microscopic changes were essentially the same in all parts of the white matter, varying only in degree. What had appeared to be punctate hemorrhages were found under low power magnification to be large rings of extravasated blood about tremendously congested small veins and capillaries (fig. 5). A closer examination of the blood vessels of the white matter

revealed changes typical of vasoparalysis. The veins and capillaries were maximally distended and congested and disclosed signs of stasis (fig. 6). The walls of the distended veins were undergoing disorganization and showed an increase of permeability for serous fluid and red blood cells. The perivascular spaces appeared distended and filled with extravasated red blood cells (fig. 6). In those areas in which the extravasation of blood was especially pronounced disruption of the

Fig. 5 (case 2).—Numerous perivascular hemorrhages. Note the distention of the perivascular spaces, which harbor large masses of extravasated red blood cells. Cresyl violet stain; × 160.

limiting glial membrane had occurred; this resulted in diffuse invasion of the adjacent nerve parenchyma by large masses of red blood cells and blood pigment (fig. 5). The cortical gray matter was fairly well preserved except for a moderate degree of edema. The leptomeninges were distended, and the pial blood vessels were congested. No signs of inflammation could be detected.

CASE 3.—A 4 week old white infant was admitted to the hospital on Nov. 23, 1944 because of severe watery diarrhea of two days' duration, associated with drowsiness and listlessness. The infant was apparently normal at birth. The mother had had syphilis. She had received 1,000,000 Oxford units of penicillin two weeks prior to delivery. The infant was first admitted to the hospital on

Fig. 6 (case 2).—A small vein and capillary of the white matter with typical signs of vasoparalysis. Note the evidence of congestion and stasis, associated with an early stage of degeneration of the vessel wall and increased permeability for red blood cells. The distended perivascular space is filled with extravasated blood. Cresyl violet; × 160.

Oct. 16, 1944 because of a diffuse cutaneous rash and a few small, scaly lesions around the penis and scrotum. Repeated dark field examinations of the lesions of the penis gave negative results, and the Wassermann and Kahn reactions of the blood were negative. The cutaneous lesions disappeared almost completely within

a few days, and the baby was apparently well until two days prior to his present admission.

On examination the baby appeared very ill, drowsy and listless. There were a severe state of dehydration, acidosis and signs of circulatory collapse. He was treated with intravenous drip of dextrose in isotonic solution of sodium chloride
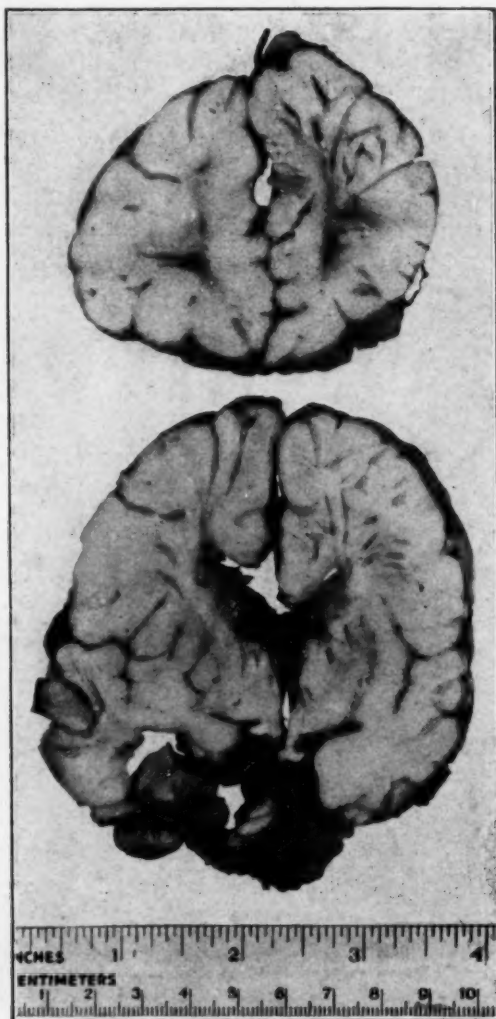
Fig. 7 (case 3).—Coronal sections through the brain, with extensive areas of hemorrhagic softening involving the caudate nucleus on both sides. Note the congestion of the central white matter in both frontal lobes.

and was given sodium bicarbonate intravenously in order to correct the acidosis. On the following day he seemed somewhat improved. The carbon dioxide–combining power was 35 volumes per cent. During the first three days the baby was afebrile. On the fourth day in the hospital the temperature began to rise and remained elevated (102 F.) until his death. He became extremely listless, apathetic

and semicomatose. On the fourteenth day in the hospital his breathing became rapid and irregular, and he died.

Autopsy.—The pathologic conditions observed, exclusive of those of the brain, were pneumonia and congestion of the liver and kidneys. No signs of syphilis were found.
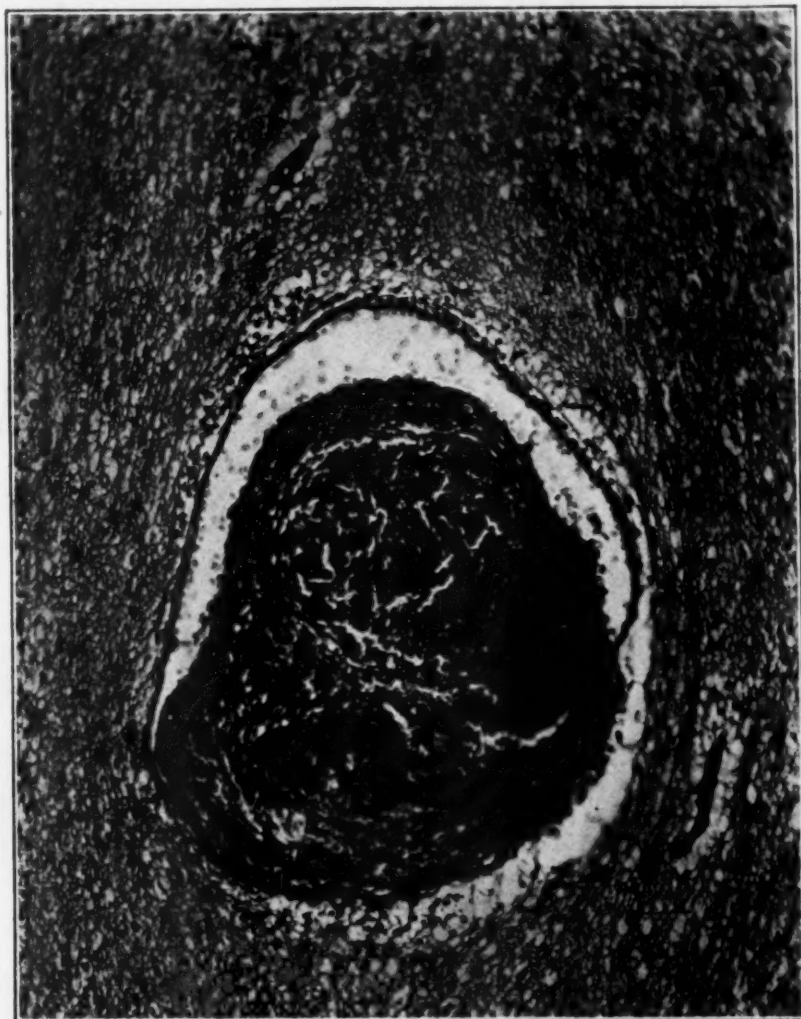
Fig. 8 (case 3).—Medium-sized vein of the white matter occluded by a thrombus. Note the absence of structural changes in the wall of the vessel. Hematoxylin-eosin stain; × 220.

Gross Examination of the Brain: The larger pial veins were found to be tremendously distended and congested. The right temporal lobe appeared very full, and there was a definite shift of the midline structures to the left. A well defined herniation of the uncus, measuring 2.3 cm. in length and 1.5 cm. in width, was present in the right temporal lobe. The configuration of the circle of Willis was normal. Coronal sections revealed extensive areas of hemorrhagic softening

immediately about both lateral ventricles, involving the caudate nuclei and the underlying striate bodies (fig. 7). The white matter of both hemispheres displayed congestion of the smaller blood vessels and numerous petechial hemorrhages. The right temporal lobe was soft to touch.

Microscopic Examination of Brain:. Histologic examination of sections taken from several areas of the gray and white matter of both hemispheres and from

Fig. 9 (case 3).—Early stage of thrombosis of a vein. The blood clot is only slightly atached to the intima. Note the rarefaction and necrosis of the surrounding nerve tissue. Hematoxylin and eosin stain; × 220.

the basal ganglia disclosed vascular lesions and alterations of the nerve tissue proper. The most striking manifestation of the circulatory disturbances was the presence of various stages of venous occlusion, as illustrated in figures 8, 9, 10 and 11. The lumens of numerous small veins were occluded with blood clots,

composed of curved strands of fibrin mixed with large masses of white and red blood cells. The clot seemed to be only slightly attached to the intima. The walls of the vessels themselves appeared well preserved. No signs of inflammation could be detected. In some of the veins it seemed possible to trace the thrombus formation from its beginning. Figure 9 shows a medium-sized vein, tremendously
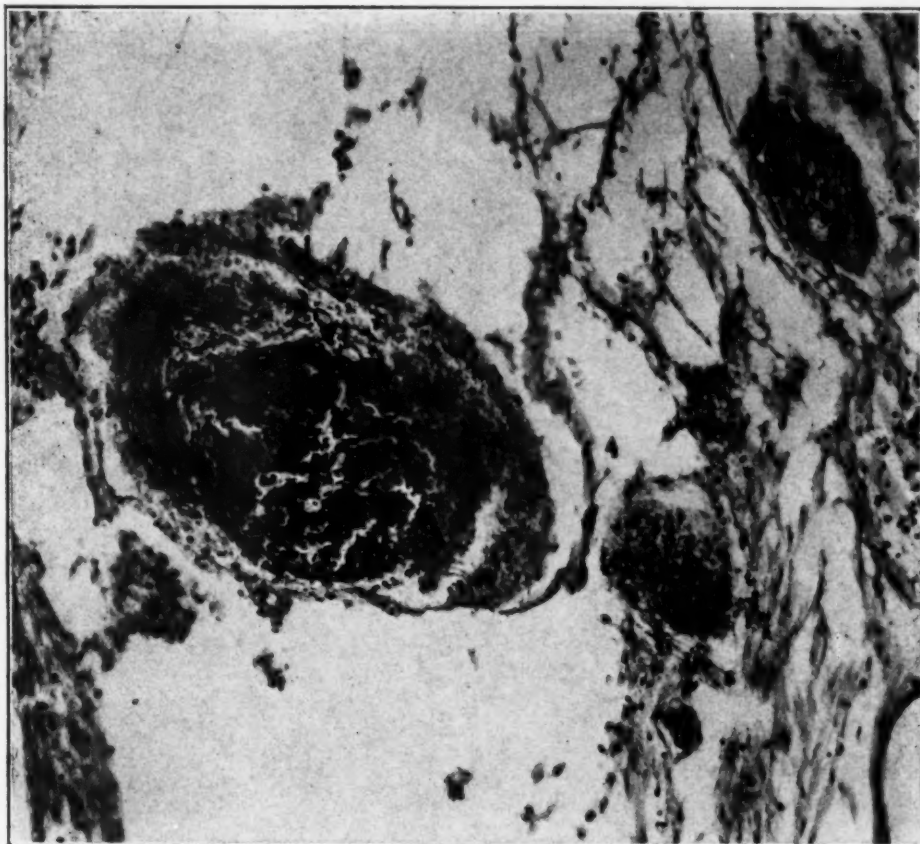
Fig. 10 (case 3).—Complete destruction of nerve parenchyma in the vicinity of a thrombosed vein. Cresyl violet stain; × 180.

distended, containing two small blood clots only slightly adherent to the intima. The wall of the vessel itself does not reveal visible structural alterations. In addition, many veins and capillaries were tremendously distended, displaying varying stages of vasoparalysis. Many of the smaller veins were engorged with blood and showed signs of stasis. Their walls disclosed an increased permeability for red blood cells, with resultant diffusely scattered perivascular petechial hemorrhages.

The changes in the nerve tissue proper consisted mainly of widely disseminated areas of hemorrhagic softening, involving chiefly the basal ganglia and the central white matter. Some of the areas of softening were circumscribed and suggested a definite perivascular distribution. In the central portion of these lesions one or more small veins displayed changes typical of vasothrombosis (fig. 10). The sur-

rounding tissue showed all signs of an acute destruction of all the constituents of the nerve parenchyma, including the glial elements. There were numerous small hemorrhages, chiefly perivascular in distribution. While these lesions, as illustrated in figure 10, represented the most frequent type of tissue destruction, characterized by complete disintegration of all tissue elements without reactive glial changes, there were a few focal areas of glial proliferation, as illustrated in
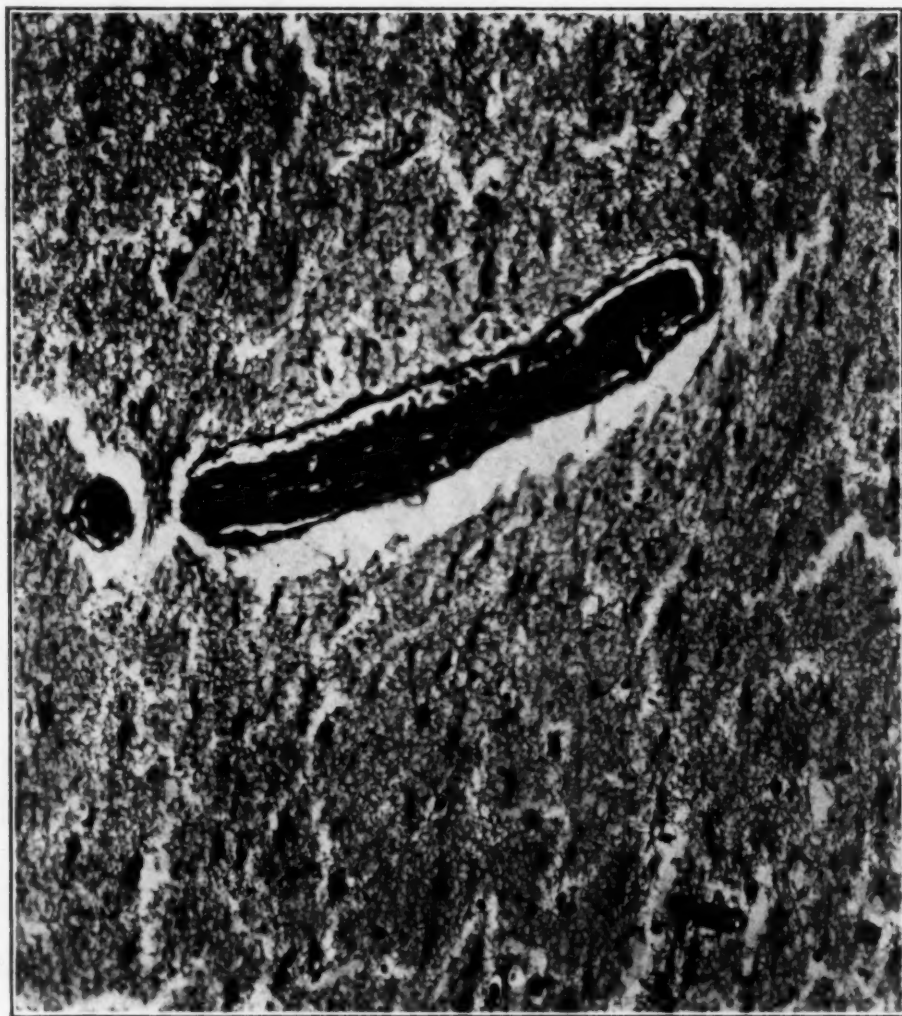
Fig. 11 (case 3).—Focal area of sclerosis of the white matter in the vicinity of a thrombosed vein. Note the diffuse proliferation of astrocytes. Hematoxylin and eosin stain; × 180.

figure 11. These focal lesions showed a diffuse proliferation of astrocytes, displaying an early stage of sclerosis and glial scar formation.

The cortical gray matter was, except for edema formation, fairly well preserved. No signs of inflammation were seen. The leptomeninges contained scattered red blood cells and a few macrophages. The pial blood vessels were

maximally distended and engorged with blood; they were occasionally surrounded with large accumulations of extravasated blood. Their walls showed no signs of structural lesions.

SUMMARY OF PATHOLOGIC CHANGES

The microscopic picture in all 3 cases displayed circulatory disturbances of varying severity. The earliest stage is illustrated by case 1; this was characterized by focal areas of perivascular transudation of serous fluid and concomitant liquefaction of the adjacent nerve parenchyma associated with regressive glial changes. The absence of visible structural alterations in the blood vessels would seem to indicate that the alterations of the nerve tissue were mainly due to an increased permeability of the vessel wall for serous fluid. A more advanced type of circulatory disturbance was found in case 2. The histologic alterations consisted in vasoparalysis of the smaller veins and capillaries with increased permeability of the vessel walls for red blood cells. This resulted in numerous perivascular hemorrhages in the subcortical and central white matter. In case 3 vasoparalysis of the smaller veins and capillaries was associated with vasothrombosis. The most pertinent changes were characterized by formation of thrombi in the tremendously distended veins and capillaries, as illustrated in figures 8, 9, 10 and 11. The alterations of the nerve tissue proper, secondary to the circulatory disturbances, consisted in case 1 in perivenous tissue liquefaction, in case 2 in focal areas of extravasation of blood and in case 3 in focal areas of tissue necrosis contiguous to the occluded veins.

It seems proper to conclude that the vascular alterations in all 3 cases are varieties of the same morbid process. The differences in the morphologic features can probably best be explained by the differences in the duration and severity of the circulatory disturbances. The formation of thrombi in case 3 might be interpreted as a late sequela of a prolonged state of vasoparalysis and was probably due to local slowing down of the circulation of the blood. The clinical data seem to corroborate this conclusion. In case 1 death occurred about forty-eight hours after the onset of the clinical symptoms; in case 2, after four days, and in case 3, after sixteen days.

In all 3 cases the circulatory disturbances were predominant in the subcortical and central white matter. The cortical gray matter was generally spared. The discrepancy between the reactions of the gray and those of the white matter of the brain can best be explained by the differences in blood supply. In a forthcoming paper the problem of selective involvement of the white matter will be discussed in greater detail. The type of change and the distribution of lesions in the brain are influenced primarily by the local structure, and particularly by its vascular supply, which is rich in the cortical gray matter and poor in the white matter.

According to Cobb, capillary counts revealed about 1,000 mm. of capillary length per cubic millimeter of tissue in the middle layers of the cerebral cortex, as compared with about 200 mm. of capillary length per cubic millimeter of tissue in the underlying white matter. Of still greater importance is the difference in the arrangement and size of the vascular tree of the white and of the gray matter. Whereas the cortical ribbon is supplied by a vascular system of the network type, formed by a tremendously dense net of capillaries, the vascular supply of white substance is composed chiefly of undivided vascular channels of considerable length; their anastomoses as compared with those of the cortex are scanty, wide meshed and more rectangular. In studies on the cerebral vascular pattern, Alexander and Putnam [3] demonstrated these differences in a convincing manner. The great majority of the larger vessels of the white matter are veins. With serial sections, Alexander and Putnam were able to demonstrate that these veins drain into the vena striae terminalis and thence into the vena magna of Galen.

The vascular alterations described as vasoparalysis and vasothrombosis involve chiefly the veins and capillaries of the white matter. Stasis and, eventually, immobilization of blood flow appear to constitute the main factor. It is obvious that the effects of retarded circulation are more apt to be observed in the poorly vascularized white matter than in the gray substance, which is richly supplied by an arborized vascular network. The absence of rich anastomoses in the white matter would facilitate the detrimental effects of stasis and would explain the selective vulnerability of the white matter for circulatory disturbances.

<div align="center">GENERAL COMMENT</div>

It is surprising how few histologic studies concerned with this type of alterations in the brain are available in the literature. In the summer of 1923 Brown, working at the Children's Hospital in Boston, observed 6 cases of rapidly fatal disease in children. In 5 of the cases necropsy revealed "intense edema and congestion of the brain." In the summer of 1929, Symmers, working at Bellevue Hospital, in New York, observed 5 cases in which the clinical and anatomic changes were identical with those encountered in Boston. Brown and Symmers [4] reported their observations as cases of "acute serous encephalitis." Unfortunately, the histologic studies were incomplete, which makes difficult a comparison with the lesions observed in the present cases. "Engorgement of the blood vessels of the brain, perivascular and pericellular edema" are mentioned as the most constant changes. In spite of the fact that

3. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. **18**:471, 1938.

4. Brown, C. L., and Symmers, D.: Acute Serous Encephalitis: A Newly Recognized Disease of Children, Am. J. Dis. Child. **29**:174 (Feb.) 1925.

no inflammatory changes were observed, the authors apparently came to the conclusion that "the disease belongs to the same general category with the so-called encephalitis lethargica." Needless to say, the clinical picture, as well as the cerebral alterations in my cases (and in cases reported by Brown and Symmers) does not warrant the assumption of any similarity with encephalitis lethargica. On the basis of my own observations, it seems proper to conclude that the condition represents a special form of damage to the brain secondary to reversible vascular disturbances characteristic of vasoparalysis and vasothrombosis.

Marburg and Casamajor [5] reported 2 cases in which extensive areas of destruction of the brain corresponding to the drainage areas of the great vein of Galen and the superior longitudinal sinus were found to be caused by venous thrombosis. The pathologic process, as well as the clinical picture, does not disclose a relationship to the present cases.

SUMMARY

In 3 illustrative cases of a rapidly fatal disease in early childhood, attended by symptoms of acute encephalitis, necropsy revealed circulatory disturbances characteristic of vasoparalysis and vasothrombosis.

In all 3 cases there were no signs of inflammation. The most striking observations were different phases of vascular alteration.

The earliest manifestations of the pathologic process were found in case 1 and consisted in focal areas of perivascular transudation of serous fluid and concomitant liquefaction of the adjacent nerve parenchyma. Since no lesions could be seen in the walls of the vessels, the pathologic process was interpreted as due to increased permeability of the vessel for serous fluid.

In case 2 a more advanced stage of vasoparalysis was displayed with increased permeability of the vessel wall for red blood cells, resulting in perivascular hemorrhages in the white matter.

The changes in case 3 were characterized by thrombotic occlusion of the smaller veins and were interpreted as late sequelae of a prolonged state of vasoparalysis.

The pathologic changes in the 3 cases appear to represent three phases of the same morbid process. The difference in their morphologic features can probably best be explained by the difference in the duration and severity of the circulatory disturbance.

Regional peculiarities of vascularization appear to be responsible for the greater vulnerability of the white substance and the relative preservation of the cortex.

Cincinnati General Hospital.

5. Marburg, O., and Casamajor, L.: Phlebostasis and Phlebothrombosis of the Brain in the Newborn and Early Childhood, Arch. Neurol. & Psychiat. **52**:170 (Sept.) 1944.

DIVERGENCE PARALYSIS ASSOCIATED WITH TUMOR
OF THE BRAIN

NATHAN SAVITSKY, M.D., and M. J. MADONICK, M.D.
NEW YORK

DIVERGENCE paralysis associated with cerebral tumor has been reported in only 5 cases, 2 of which were verified. Straub [1] reported the case of a 20 year old woman with bilateral papilledema, involvement of the left trigeminal, facial and acoustic nerves and bilateral nystagmus. The author's diagnosis was "tumor" of the middle fossa. Howard [2] described the case of a woman aged 71 who had had a carcinoma of the breast removed five years previously. She complained of diplopia for two months prior to the examination, which revealed divergence paralysis. Multiple areas of destruction of the bony cranial vault and the sella turcica were observed in the roentgenograms. The diagnosis was "metastasis of the carcinoma to the supposed divergence center." Holden [3] mentioned seeing divergence paralysis in a case of "mid-brain tumor" but gave no clinical data. These 3 cases were not verified by operation or necropsy. Lippmann [4] recently described the case of a youth aged 20 who had had divergence paralysis for about two years with cerebellar signs, especially on the left side. At operation a cerebellar tumor was found and partly removed, but the patient died. Bender and one of us (N. S.) [5] reported a case of a small vascular tumor in the pons. Divergence paralysis was the chief complaint during life.

We report 4 additional proved cases of tumor of the posterior fossa, 2 of cerebellar tumors and 2 of acoustic neuromas. Divergence paralysis probably occurs more frequently than is indicated in the literature. A review of a report of a large series of tumors of the posterior fossa

1. Straub, M.: Ueber Lähmung der Divergenz, Centralbl. f. prakt. Augenh. **21**:8, 1897.

2. Howard, H. J.: Divergence Paralysis, Am. J. Ophth. **14**:736, 1931.

3. Holden, W. A.: The Ocular Manifestations of Epidemic Encephalitis, Arch. Ophth. **50**:101, 1921.

4. Lippmann, O.: Paralysis of Divergence Due to Cerebellar Tumor, Arch. Ophth. **31**:299 (April) 1944.

5. Bender, M. B., and Savitsky, N.: Paralysis of Divergence, Arch. Ophth. **23**:1046 (May) 1940.

(Cushing,[6] Henschen [7] and Olsen and Horrax [8]) reveals the occasional mention of diplopia with no evident ocular palsies or impairment of conjugate gaze. Precise analyses of these unclear cases of diplopia are usually lacking. The present investigation leads to the conclusion that more careful study of some of these cases would probably have indicated the presence of divergence paralysis. This divergence paralysis can easily be detected with the red glass test. There was no evidence of weakness or paralysis of the external rectus muscle in any of the present cases.

REPORT OF CASES

CASE 1.—A woman aged 22, single, was admitted to the Mount Sinai Hospital because of pain in the back of the head and vomiting of six months' duration. The vomiting was projectile and had persisted from the onset to about two months prior to her admission. Diplopia on looking at a distance appeared three weeks before she entered the hospital. During the week preceding her admission vomiting reappeared, and the pain in the neck had increased in severity.

On examination a bony protrusion was palpated over the right occipital bone. The gait was broad based, with a tendency to veer to the right. There was slight tilting of the head to the right, and the neck was held stiffly. Bilateral papilledema with hemorrhages and exudates, lateral nystagmus and occasional horizontal nystagmus were observed. There were pass pointing and drift of the right upper extremity.

Lumbar puncture revealed a slightly xanthochromic fluid, with an initial pressure of 220 mm. of water and a total protein content of 33 mg. per hundred cubic centimeters. Roentgenographic study of the skull was disturbing in that there seemed to be a large bony defect in the floor of the middle fossa. Because of this the nasopharynx was examined for a tumor, but none was found. Ventriculographic examination revealed bilateral internal hydrocephalus without a shift. A suboccipital craniotomy was carried out, and a large cyst was encountered in the right cerebellar lobe and extending into the tonsil, which was herniated through the foramen magnum. The arch of the atlas was removed, and at the tip of the tonsil a tumor was found which formed the mural nodule of the cyst. The diagnosis was hemangioendotheliomatous meningioma, and removal was complete.

The postoperative course was marked by slight paresthesias in the left hand. The patient improved but showed slight papilledema at the time of her discharge, on March 11, 1943. The diplopia and the divergence paralysis disappeared soon after the operation.

CASE 2.—A woman aged 54 was admitted to the Mount Sinai Hospital on Oct. 21, 1943, with a history of nausea, vomiting, headaches of about three weeks' duration and buzzing in the left ear since September 1941. During August

6. Cushing, H.: Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle, Philadelphia, W. B. Saunders Company, 1917, p. 165.

7. Henschen, F.: Ueber Geschwülste der hinteren Schädelgrube, insbesondere des Kleinhirnbrückenwinkels, Jena, G. Fischer, 1910.

8. Olsen, A., and Horrax, G.: The Symptomatology of Acoustic Neuromas, with Special Reference to Atypical Features, J. Neurosurg. **1**:371, 1944.

1941 she had had transient "weak spells." In February 1943 blurring of vision was noted and she began to see double at a distance.

On examination there were bilateral papilledema, lateral nystagmus on looking to the right and left and drift of the right upper extremity. Hearing was impaired on the left side. Divergence paralysis was demonstrated with the red glass test. There was no evidence of weakness of the external rectus muscle. The caloric test indicated no response on the left side. The electroencephalographic pattern was normal. A ventriculogram demonstrated symmetric dilatation of the ventricular system with cutting off of the tip of the left temporal horn.

At operation a perineural fibroblastoma was removed from the left cerebellopontile angle. The divergence paralysis disappeared after the operation, and the patient was discharged eight weeks after admission.

CASE 3.—A man aged 51 first complained of double vision while playing golf in August 1943. He began to have attacks of pain in the back of the neck with radiation to the left temple several times a day. During the night before he was examined he had sharp pain on the top of the head.

Examination, on Oct. 19, 1943, showed bilateral papilledema, clockwise rotatory nystagmus on looking to the left, divergence paralysis, a diminished left corneal reflex and diminished bone conduction on the left side. Bone conduction was better than air conduction bilaterally. There was an old perforation of the left ear drum. The patient had a history of inability to hear with the left ear for fifteen years.

On Nov. 2, 1943 there was increasing bilateral papilledéma with hemorrhages and exudates. On November 12 there were spontaneous outward pass pointing to the left; concentric constriction of the visual fields with enlarged blindspots; bilateral ataxia in the heel to knee test, more marked on the right, and hyperreflexia with a positive Babinski sign on the left side. There was still bilateral papilledema with rotatory nystagmus on looking to the left. Hearing was almost entirely lost on the left side, and caloric responses were absent on that side. Divergence paralysis persisted, with no evidence of involvement of either external rectus muscle.

At operation, on November 23, an acoustic neuroma was removed on the left side. Transitory palsy of the sixth nerve and weakness of the lower part of the face appeared on that side after operation. Slight ataxia in the heel to knee test and a Babinski sign were present on the left side. The divergence paralysis disappeared, and the hemorrhages in the retinas cleared up soon after the operation. On Jan. 24, 1944 there were no complaints except for slight dull headache.

CASE 4.—A white man aged 54 was admitted to the Montefiore Hospital on July 11, 1945, complaining of inability to stand or walk for three months. Headaches and double vision appeared during June 1941. About that time he first noted that his gait was unsteady. Several days later frontal and retro-orbital headaches appeared, which were intensified on his lying down and were somewhat relieved by his tilting his head to the right. He also complained of occipital and nuchal pain. A week later he noticed slight weakness of the left hand and double vision in all directions.

He was admitted to the Mount Sinai Hospital on July 18, 1941. Examination revealed a deformity of the occipital region of the skull. The occiput was flattened. The gait was wide based, with a tendency to veer to the right. Bilateral dysdiadokokinesis, spontaneous pass pointing to the left, slight ataxia of the left lower limb, bilateral papilledema, bilateral diminution of hearing,

nystagmus in all directions and a slightly more active knee jerk on the left side were observed. There were no palsies of the external ocular muscles.

Electroencephalographic study suggested an expanding lesion in the posterior fossa. Ventriculographic examination showed symmetric dilatation of the lateral ventricles. Operation exposed a large vascular tumor occupying the vermis and the adjacent portion of both cerebellar lobes, especially on the right, with projection of the tumor into the spinal cord. Because of the extreme vascularity, radical removal was not attempted, and only a biopsy was done.

The clinical picture at present consists in bilateral cerebellar signs in the upper and lower limbs, nystagmus, cerebellar speech, slight hyperreflexia and a positive Babinski sign on the right side, inconstant divergence paresis and bilateral papilledema. There is no evidence of weakness of the external rectus muscle.

In a case previously reported by 1 of us (N. S.),[5] a tumor was found within the brain stem. It was assumed that the region of the divergence center had been involved by the neoplasm. In the 4 cases reported in this paper and in Lippmann's case there was no clinical evidence of disease of the brain stem. In each of the present 4 cases a tumor of the posterior fossa was found at operation. We have not yet encountered a supratentorial tumor with divergence paralysis, though false localizing signs in the brain stem have been reported with such tumors (Nielsen and Hollenbeck[9] and Pichler[10]). We have thus far not found divergence paralysis in cases of increased intracranial pressure without tumor or in cases of intraventricular tumors. In the absence of any available anatomic studies of the brain stem in such cases, a definite opinion regarding the pathologic changes in the pons cannot be given.

CONCLUSIONS AND SUMMARY

We add 4 cases of divergence paralysis associated with cerebral tumor to the 5 cases recorded in the literature.

Cranial exploration in all the cases revealed a tumor of the posterior fossa.

We believe this divergence paralysis is the result of involvement of the divergence center in the brain stem in some way.

The divergence paralysis may be inconstant.

The divergence paralysis disappeared in the 3 cases in which the tumor was successfully removed.

1882 Grand Concourse (57).

9. Nielsen, J. M., and Hollenbeck, A. E.: A Case of False Localizing Signs of Cerebral Neoplasm, Bull. Los Angeles Neurol. Soc. **5**:124, 1940.

10. Pichler, E.: Zur Frage der Bedingtheit irreführender Symptome bei Grosshirntumoren, Arch. f. Psychiat. **110**:75, 1939.

COMBAT NEUROSES
Development of Combat Exhaustion

ROY L. SWANK, M.D.
BOSTON
AND
WALTER E. MARCHAND, M.D.
NEW YORK

IN World War II the neuroses which result from combat have been designated as "combat exhaustion." This terminology implies two fundamental things: First, these neuroses are due primarily to combat, and, second, they develop after a period of combat sufficiently long to produce a significant degree of exhaustion.[1] Through misunderstanding many people use the term indiscriminately, and confusion has arisen; they include under this head the neuroses which develop during the first few days of combat, and even the disorders of behavior of men who have never experienced actual combat. The usefulness of this term in distinguishing the more stable and willing from the unstable and unwilling personalities is thereby lost. This is unfortunate, since a substantial percentage of men are of the former type and have broken down under conditions of continuous long and severe stress which infrequently, if ever, obtained before. The number of early breakdowns has been reduced by a better selection of personnel on induction, followed by the further "weeding out" of potentially weak and unwilling persons during basic training and in battle simulation exercises prior to actual combat.

The present paper is a description of combat neuroses, in an attempt to clarify the syndrome or syndromes of combat exhaustion and their relationship to neuroses in general. Although emphasis will be placed on one unit and the men in it who remained longest in combat, observations on many other units will be included, and the problem in general will be considered. For orientation, the behavior of the men during the period immediately prior to combat will be discussed. This section will be followed by a description of, first, the behavior of soldiers in combat and, second, the changes in behavior which these men undergo during the first week or so after evacuation from combat.

---

1. Hereafter in this paper the designation "combat exhaustion" implies that these two factors are present.

BEHAVIOR DURING THE PERIOD OF "ALERT" PRIOR TO COMBAT

The duration of this period was no doubt variable, but for the unit under observation it was approximately eighty days.

Most men exhibited feelings of insecurity and irritability. First, there was an increase in difficulties concerned with domestic life and courtship arising from failure of people at home to respond to the soldier's increasing demands for declarations of love and fidelity. Secondly, many men who had seldom or never gone to church or sought religious solace became very religious and exhibited improved moral behavior in preparation for the possibility of death. Third, the soldier frequently expressed the sentiment, by word or in letters, that, although his comrades might become casualties, he would come through alive. In contrast to this major group, a few men, although well disciplined before, assumed a "devil may care" attitude toward Army regulations and superior officers and became morally delinquent. This attitude is expressed in the words: "The worst that they can do is to shoot me, and I'm going to be killed anyway."

During this period there was an increase in the number of functional complaints, chiefly dyspnea, palpitation, weakness, abdominal pain, vomiting and backache. Many men were hospitalized for these disturbances and were not returned to the unit. There was also an increase in the number of self-inflicted wounds, which resulted in a further loss of personnel. Lastly, malingering, either through self injury or through a display of physical inaptitude during preinvasion amphibious exercises, was responsible for the loss of a few men from the unit. The total loss of man power through the aforementioned means was not great and represented the final screening of men unfit for combat.

Obvious generalized anxiety was first noted when the unit was told that it would take part in the assault on the Continent. During the ensuing months, however, the men became adjusted to the role they were to play; their anxieties subsided and were not observed again until embarkation. During the crossing of the Channel generalized restlessness was in evidence, but there were no actual displays of fear until the men went "over the side" to assault craft in a rough sea prior to H-hour. The men then crowded toward the rear of the craft in search of safety against striking a floating mine or an underwater obstacle. From that point on life was to consist of a series of dangerous situations, each accompanied with new anxieties or fears which had to be overcome.

BEHAVIOR DURING COMBAT

Development of Combat Exhaustion.—During the first few days of combat the men were in a constant state of fluctuating fear. They had

urinary frequency and urgency, intense thirst, anorexia, and even a fear of eating, a fear of being left alone or of exposing themselves, even to defecate, and an increase in sweating. During acute incidents, palpitation, an increase in sweating, vasomotor instability and the overt signs of fear, such as tremulousness, became more or less universal. Many men became selfish to the point that they took food, blankets, entrenching tools and similar articles from others for their own use. This soon stopped, however, when they realized that individual survival was dependent on survival of the group, and cooperation, to the point of self deprivation, continued throughout the ensuing period of combat.

Gradually the men became adapted to the existing conditions of battle. They became familiar with the sounds of their own, as contrasted with the enemy's artillery and automatic small arms weapons. From the sound they could determine the caliber of artillery fire and
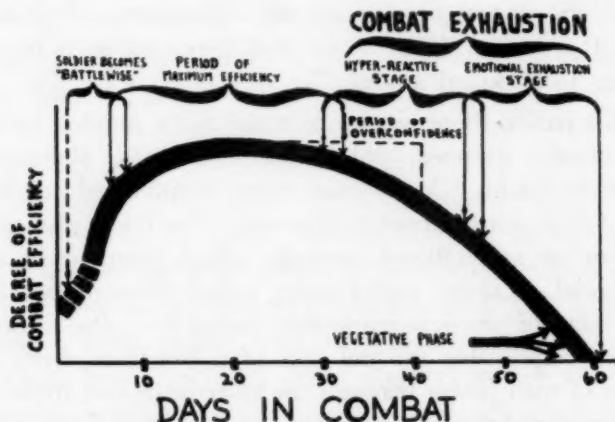
Graphic portrayal of the relation of stress and the development of combat exhaustion to the combat efficiency (heavy black line) of the average soldier.

how close the projectiles would fall, thereby knowing when to "hit the dirt." Without being conscious of it, they chose paths of approach which afforded concealment and cover, and they constantly watched for snipers in trees and hedges. Smoke and fire discipline at night became automatic, and the soldier was always well oriented to his own and the enemy's strength and position. These significant, yet subtle, changes, as well as many others, constitute the state of "battle wiseness," without which the soldier does not survive to become efficient in combat. Concurrently, the physiologic reactions to danger, referred to before, became modified or controlled to the point that they no longer hindered the soldier in combat. Short periods of overt anxiety appeared from time to time after this in the face of unexpected dangers or developments, e. g., the use of "new weapons" by the enemy, but these rarely

developed to the stage that was harmful, and they were soon brought under control again.

The large majority of men achieved adequate adjustment in approximately five to seven days. By that time they had become efficient in combat and could rightfully be considered "battle wise." Further, and slow, improvement followed, peak efficiency as a combat soldier being reached about D plus 21 day. This held for approximately one week longer, the entire period of maximum efficiency in battle lasting about three weeks. The majority of men then showed a gradual and steady decline in efficiency, attended by the development of abnormal psychologic and emotional reactions. In a few over-confident ones, however, high efficiency in combat was prolonged for a short period. These men felt that they were immune from danger; they exposed themselves unnecessarily, and they were especially aggressive in battle. Their casualties were high, and the few who were not killed soon adopted the general behavior of the group. This will be described now.

The first symptom of combat exhaustion made its appearance at about D plus 25 to D plus 30 day in most soldiers. This was an abnormal fatigability, which could no longer be relieved by periods of rest up to forty-eight hours. The fear reactions, so noticeable early in combat, and so successfully controlled during the period of high efficiency in battle, reappeared more frequently and were quelled with less success. Unconsciously, the soldier lost confidence in himself. This was clearly shown in his reactions toward various battle stimuli. He began to lose the fine points of discrimination in which he had prided himself. He no longer could tell the difference between friendly and enemy artillery and mortar fire and referred to all as the fabulous "eighty-eight."

To all these stimuli his reactions became excessive, often to the point that they were harmful. He became overcautious; he stayed close by or in his slit trench whenever possible; he walked rather than rode in a vehicle, so that he would be able to get to cover more readily; and he became a "follower" rather than a leader. Sleeplessness became evident early and persisted despite his mounting exhaustion. If he slept at all, it was during the hours of daylight, because of a greater feeling of insecurity during the hours of darkness. A feeling of insecurity was also shown by the fact that he repeatedly wanted to "know the situation," i. e., the disposition of the enemy, the availability of supporting troops and the Allied success in dealing with the enemy. Some degree of irritability also made its appearance. This was shown in mild form by his statements that the campaign was being run poorly and that things in general were not working out as smoothly as they had once. The blame for this was always placed on other units,

which he felt were not performing their mission, or on some higher headquarters, which did not "know the score." In more severe form, the irritability consisted in "blowing his top" over matters which at one time would have left him unconcerned. Restlessness was usually present and often became so extreme that he had difficulty remaining in his slit trench even when under fire. Anxiety concerning himself, both directly and remotely, became progressively in evidence during this period; the facies associated with fear and anxiety became progressively more apparent and persistent, and tremulousness came to be ever present.

As the casualties mounted and his old friends became conspicuous by their absence, he was increasingly aware of his dwindling chances of survival, and a feeling of hopelessness became evident. This was expressed by such remarks as: "I guess I'll get mine tomorrow"; "We [meaning the unit] can't keep going like this"; "They'll wipe us out sooner or later," and "I might as well get hit now and get it over with." This evident hopelessness, however, was transient rather than fixed, as indicated by his recognition that should the type of warfare change from static to fluid there would be a chance for survival.

The type of warfare did not alter, and the pace of advance remained the same. During the period of D plus 40 to D plus 45 day a group of symptoms which will be referred to collectively as "emotional exhaustion" first made their appearance. These are characterized by a general slowing of mental processes and apathy, in contrast to the hyperactivity and marked anxiety which had been present before. The men became resigned to the state in which they found themselves, and as far as they were concerned the situation was one of absolute hopelessness. They saw no means of overcoming or getting beyond the state of things, only that it was meant for them to "sweat it out." The thought and hope of surviving combat were now foreign; one thing to them was certain, they would be killed. Should they be lucky, they would be merely wounded. The influence and reassurance of capable and understanding officers and noncommissioned officers failed now to arouse these soldiers from their feeling of hopelessness.

Symptoms which had been developing insidiously now became evident. The soldier was slow witted; he was slow to comprehend simple orders, directions and technics, and he failed to perform even life-saving measures, such as digging in quickly. Memory defects became so extreme that he could not be counted on to relay a verbal order. There was also present a definite lack of concentration on whatever task was at hand, and the man remained preoccupied for the most part with thoughts of home, the absolute hopelessness of the situation and death. This constant dwelling on death did not indicate a state of fear but,

rather, a certainty that it would occur. The anxious stare, together with the tremulousness and generalized hyperactivity, was replaced gradually by an emotionless expression, lassitude and listlessness.

Some men exhibiting the picture just described were not evacuated, and all such symptoms became intensified to the point that the soldier became practically nonreactive both physically and emotionally. He could then best be described as one leading a vegetative existence. His facial expression was one of complete apathy: a nonsmiling, rigid-faced person with lusterless eyes. His body was seemingly helpless, movements being performed with an effort. The soldier was in a semistuporous state, difficult to arouse from his reverie; he remained almost constantly in or near his slit trench, and during acute actions he took little or no part, trembling constantly.

A soldier with combat exhaustion usually continued in battle until he was exposed to an acute and severe "incident," such as a "near miss" from artillery or mortar fire or a heavy artillery barrage. In many instances a close friend was often killed before "his very eyes." This usually provoked a violent emotional explosion, and the soldier became disoriented and confused. Often he ran about wildly and aimlessly, with a total disregard for danger, rolled on the ground and cried convulsively. For this episode and the succeeding evacuation to an aid station he was usually amnesic, totally or in part. In some instances he remained stuporous, prostrate, amnesic and unable to talk or hear clearly for days, and in this state he arrived at a general hospital. Noises which were associated with danger, i. e., airplanes and gunfire, provoked violent trembling and agitation. This behavior sometimes lasted for weeks, being temporarily relieved by sodium amytal or pentothal given intravenously, at which time the soldier's past and combat history could be readily elicited. With the end of this short narcosis he returned to the stuporous, confused, amnesic state which existed before.

Other Psychologic Reactions Which Necessitated Evacuation From Combat.—As might be expected, a number of men failed to adjust themselves during the first or the succeeding weeks of combat. These men fell into several groups. One group became panicky or terror stricken at the first sign of danger. Even a minor small arms skirmish with the enemy; a single artillery barrage, bombing or strafing; a night attack, or a counterattack caused them to become suddenly disoriented, confused and amnesic. They ran around wildly, even toward the enemy's line or the artillery impact area. Some fell to the ground, clawing the earth, or, finding a slit trench, remained there, crying and trembling, impossible to control. A short period of sedation in the

rear and reassurance quickly quieted most of them, and a number returned to combat. Many of them, however, had to be evacuated from the combat area, where they improved rapidly to an apparently normal state when reassured that they need not return to combat. Their tolerance for danger remained low, and they displayed fear or anxiety when enemy, or even friendly, aircraft were overhead or during periods when rumors were rampant. In a second, and smaller, group of men conversion symptoms developed, during this early period of combat, such as paralysis of an arm or visual defects. The prognosis for their recovery from the immediate hysterical manifestation was usually good, but for a return to combat it was very poor.

Few somatic complaints were noted during the first few days of combat. These became more common after two or three weeks of combat and consisted primarily of abdominal pain and vomiting, backache and headaches. More often than not, when incapacitated by these symptoms, either the soldier had suffered from the same trouble in civilian life, or there was some anatomic basis for his trouble. In veteran soldiers these somatic complaints, especially abdominal pain, were probably more common. Yet they were seldom disabling, and they attended the anxiety and psychologic symptoms of combat exhaustion present in most troops of the unit under consideration after thirty days of combat. As a rule these soldiers seemed to have insight into their troubles, and reassurance usually satisfied them. A few veteran soldiers had severe abdominal pain and vomiting but attributed this to the C or K rations which they had existed on for weeks, and even months.[2]

Conversion hysterical symptoms were also unusual in the veteran combat soldier. One case of foot drop, 1 case of gross paralysis of a leg, several cases of aphonia and several of deafness are remembered. It was the impression that previous organic disease was simulated in most of these cases. Amnesia was seen in veteran combat troops rarely, if at all, except in men who were confused and emotionally exhausted or in men suffering a blast concussion.

CHANGES IN BEHAVIOR WHICH OCCURRED DURING THE FIRST WEEK AFTER EVACUATION FROM COMBAT

Men who had broken down early in combat or who had never adjusted to combat usually appeared very anxious or fearful. Their

2. These diets are recognized as having low thiamine contents, and it has been recommended that they be supplemented with foods rich in vitamins if consumed for longer than five days ("Messing in the ETO," prepared by the Office of Chief Quartermaster, Headquarters, Services of Supply, European Theater of Operations of the United States Army, February 1944).

anxiety appeared superficial, and diversion or the assurance that they would not be returned to combat quickly quelled their uneasiness. The few calm persons in this group were greatly disturbed by threats of combat. The few with hysterical paralysis, deafness and similar symptoms remained quite unperturbed.

By far the majority of patients were victims of combat exhaustion. All these men were tense, sleepless, irritable and fearful of noises simulating combat, and almost all suffered from dreams of combat. Most complained of various somatic symptoms, but these were rarely incapacitating. Two subgroups were readily identified, although most of the patients exhibited symptoms of both. The patients in one group were very anxious, hyperactive, both mentally and physically, and restless. Some were emotionally unstable to the point that they became angry or cried at the slightest provocation or became irritated and uncompromising toward their best friends for similar trivial reasons. These men represented the early, or beginning, phase of combat exhaustion, i. e., the hyperreactive phase. The patients in the second group were dull and listless; they were preoccupied more or less of the time, were retarded mentally and physically and in some instances appeared apathetic. These men represented the later phase of combat exhaustion, i. e., the phase of emotional exhaustion. Only a few patients remained semistuporous, prostrate, amnesic and extremely agitated by sudden noises. In short, most men exhibited the essential features of combat exhaustion. The anxiety, retardation and other psychologic changes had all lessened in intensity, probably as a result of the narcosis therapy which they had received forward and the relative quiet and security of the hospital. One feature was noteworthy. In this period of seven to ten days many of the very retarded, preoccupied and apathetic patients changed to appear anxious and showed definite evidences of increasing brightness, increasing ability to concentrate, increasing motor activity and diminishing preoccupation. At this time also, a number of men began to show evidence of mild depression of mood.

COMMENT

It is necessary for the reader to understand clearly that the foregoing description applies to the average soldier in the unit under observation. Other factors being equal, it is recognized that individual tolerance for battle stress varies. Combat exhaustion may appear in as few as fifteen or twenty days or in as many as forty or fifty days instead of in approximately thirty days, as it did in the majority of men. One thing alone seems to be certain: Practically all infantry soldiers suffer from a neurotic reaction eventually if they are subjected to the stress of modern combat continuously and long enough. True as this

statement appears to be, an occasional soldier seems capable of with-standing combat for an inordinate length of time. Perhaps less than 2 per cent (as judged by numerous conversations with veteran soldiers) fall into this class.[3] No personality type dominates this small, "abnormal," group, but it is interesting that aggressive psychopathic personalities, who were poorly disciplined before combat, stand out.

The fact that some men continued in combat for one hundred to one hundred and fifteen days, and even longer, is likely to be misleading. Near D plus 55 day static warfare was replaced by fluid warfare. The Allied forces broke through the enemy's lines, and many units broke out into the open and made rapid and satisfactory progress. Under these conditions many men on the verge of breakdown appeared to improve, or merely carried on temporarily. When the enemy's resistance became organized again, especially when these men were subjected to heavy artillery fire and were "pinned down," all symptoms of combat exhaustion flared up, and the long-awaited breakdown followed. The fact that the exploitation of the break through was accomplished with a maximum physical effort and that the subsequent period, when units were "pinned down," was accompanied with a minimum physical effort, indicates the relative unimportance of factors of physical stress in the production of combat exhaustion.

, Another extremely variable factor, possible of being misleading, is the stress of combat itself. In the Normandy campaign, from D-Day until the break through, this stress was continuous and severe. Rests were infrequent and usually for no longer than one day. Particularly severe was the last part of the campaign. Each hedgerow had to be fought for and "sweat out." Casualties occurred daily at a rate which convinced even the most confident soldier that death or mutilation was certain unless the type of warfare changed. In the unit under consideration the casualty rate was about average for the combat infantry units in that campaign. Several other units were less fortunate and had casualty rates much higher. In these units the symptoms of combat exhaustion developed much more quickly. In another unit with a lower than average casualty rate fewer cases of breakdown were seen, and these developed only after a much longer period of combat.

The character and development of combat exhaustion also varied somewhat with the intensity of the stress. The term "stress" is used here in a general way. In practice, however, the casualty rate and

---

3. This seemed true when this paper was written, in November 1944. Since then we have concluded that all normal men eventually suffer combat exhaustion in prolonged continuous and severe combat. The exceptions to this rule are psychotic soldiers, and a number of examples of this have been observed.

its implications were by far the most important factors. In units with a higher or lower than average casualty rate, the stages of behavior through which the combat soldier passed were likely to be less distinct. In the former, the soldier might never adjust himself to combat, and in a period of from fourteen to twenty-one days there might develop a neurosis comparable to the hyperactive stage of combat exhaustion without his first becoming "battle wise" or efficient in combat. In the latter, the stage of anxiety, or hyperreactivity, was frequently passed over without being noticed, emotional exhaustion developing insidiously. Here, again, it should be clear that the response of different soldiers to the same stimulus was not always the same. Hence, great individual variations within units were noted.

Most men who suffered from a neurosis (probably about 70 per cent) were evacuated from combat immediately after an acute "incident." Early in combat, small arms fire, a single aircraft strafing or a short artillery barrage constituted an acute incident. In the veteran soldier a much stronger stimulus was usually required, e. g., a heavy artillery barrage or a near miss from artillery fire or mortar shell or bomb. The mechanism by which these "acute incidents" precipitated neurotic reactions is not clear, but the following explanation, although crude, is offered.

In many cases the stimulus was psychologic and should be considered as an acute exacerbation of battle stress, a terrorizing experience. Men so affected were usually dazed, confused and uncontrollable but were seldom unconscious. In a smaller number of men real concussion probably occurred, resulting either in physiologic or in anatomic damage to the nervous system and its exteroceptive nerve endings, as well as to other parts of the body. Men so affected usually heard the concussing blast and sensed vaguely that they had been blown through space. For subsequent events they were completely amnesic or dazed for a varying period, and often it was reported that they had been unconscious. They recovered consciousness at an aid station or farther back of the line and discovered that their hearing was impaired, that there was a constant buzzing in one or both ears or that they had a headache and were dizzy. Many had bled from the ears, nose and/or mouth. Pains in the chest and other symptoms due to blast might be present. Frequently one or both tympanic membranes had been ruptured. Recovery from the effects of blast was slow; but as this occurred symptoms of combat exhaustion usually became increasingly evident. It was possible usually to determine that the soldier had suffered from some symptoms of combat exhaustion before the blast, and the evidence was strong that, in addition to physiologic and possible anatomic effects,

psychologic trauma had also occurred and had intensified the neurosis. In most instances the symptoms of blast referable to the nervous system cleared in one to three or four weeks. In a few cases, however, these symptoms persisted for as long as twelve months; possibly in those instances there was anatomic damage to the nervous system. It is interesting that some men with symptoms of severe concussion due to blast exhibited no evidences of combat exhaustion.

The recognition and evaluation of combat exhaustion may be difficult by virtue of the changes which occur in its symptoms and its apparent similarity at times to normal fear reactions. The first reaction of the average soldier to combat was one of anxiety and fear. This became controlled in the "battle-wise" soldier. Later, the soldier appeared to lose this ability to control his emotions, and anxiety reappeared in a somewhat similar form. The violence of these emotional and physical reactions gradually diminished, and a general slowing down of all mental and physical processes, not accompanied as a rule with mood depression, developed. The final picture was one of apathy, with pronounced physical and mental retardation. This we have chosen to refer to as emotional exhaustion, since the mood response to ordinary stimuli is weakened or absent. There is a definite similarity of this picture to that of schizophrenia, and the condition of many of these patients was so diagnosed before they arrived at the general hospital. In the hospital a slow regression of symptoms occurred. The patient became more active mentally and physically, and his mood response to ordinary stimuli increased in intensity. In most patients the anxiety reappeared, but in many a definite, but mild, depression became evident. As the neurosis became more chronic, mood depressions became more frequent; but rarely were they severe.

Despite this changing picture, the breakdowns early in combat and the early manifestations of combat exhaustion are usually recognized with ease. This statement applies also to the extremely retarded and apathetic soldier. Unfortunately, in a significant number of men symptoms develop so insidiously that they are not evacuated until after an "acute incident." By the time these men arrive at a general hospital, either spontaneously or as the result of receiving narcosis therapy forward, they have recovered their composure and appear slightly anxious. Frequently they are without insight into the nature of their condition. Careful observations reveal, however, that they are retarded, preoccupied, lacking in ability to concentrate and in other ways very ill. Too often this state is overlooked entirely or is mistaken for a constitutional defect. The results of adequate physical therapy and a knowledge of the man's combat history are sufficient in most instances to correct this impression.

SUMMARY

The behavior of combat soldiers who took part in the assault on Normandy is described and discussed. The development and characterization of combat exhaustion are outlined, and the relation of this condition to neuroses in general and to blast concussion is noted. The effect of the severity and duration of combat stress on the symptoms and their mode of development are emphasized.

Boston City Hospital.

NEUROFIBROMATOSIS WITH DEFECT IN WALL OF ORBIT

Report of Five Cases

WILLIAM T. PEYTON, M.D.

AND

DONALD R. SIMMONS, M.D.

MINNEAPOLIS

SINCE von Recklinghausen described neurofibromatosis in 1882 there has been a radical change in the concept of this disease. It is now well recognized that the cutaneous tumors and the pigmentation, as described by von Recklinghausen, are only two manifestations of a congenital defect which, in its widespread involvement, may affect practically any or all of the systems of the body.

HEREDITY

The hereditary nature of neurofibromatosis has been conclusively established, but Preiser and Davenport [1] have shown especially well that its inheritance follows regular mendelian principles and that the hereditary factor controlling it is a dominant one. They collected 30 cases from the literature in which 2 or more members of a family were affected. Uhlmann and Grossman [2] examined 60 members of 3 families with Recklinghausen's disease and found evidence of the disease (either tumor formation or pigmentation) in 13 of these persons. In 1 family members of three generations were observed and found to have lesions of striking similarity. Stahnke [3] pointed out that the whole disease may be considered a congenital anomaly and that spina bifida, hypospadias, glaucoma and elephantiasis are only a few of the congenital defects commonly associated with neurofibromatosis. Thus, it would appear that the cause of the disease usually lies in defective germ plasm.

HISTOPATHOLOGIC FEATURES

There has been some difference of opinion as to the cellular origin of the neurofibroma. Masson [4] stated the belief that this tumor is

1. Preiser, S. A., and Davenport, C. B.: Multiple Neurofibromatosis (von Recklinghausen's Disease) and Its Inheritance, with Description of a Case, Am. J. M. Sc. **156**:507, 1918.

2. Uhlmann, E., and Grossman, A.: Von Recklinghausen's Neurofibromatosis with Bone Manifestations, Ann. Int. Med. **14**:225, 1940.

3. Stahnke, E.: Ueber Knochenveränderungen bei Neurofibromatose, Deutsche Ztschr. f. Chir. **168**:6, 1922.

derived from the sheath of Schwann cells and proposed the term "schwannoma" as a more fitting term than neurofibroma. He substantiated his contentions with experimental work on animals. Penfield and Young,[5] on the other hand, expressed the belief that the tumor does not arise from nerve tissue but that it is produced from fibroblasts and preserves the peculiar characteristics of connective tissue. It is made up of collagen fibers which stain selectively with reticulin stains; in addition to this selectivity in staining reaction, the fibers possess morphologic characteristics which mark them as distinctively connective tissue, rather than nerve tissue, inasmuch as there are no fusiform enlargements or collaterals. In addition, when this tumor becomes malignant, it gives rise to sarcoma.

If it is true that the neurofibroma arises from mesenchyme, it is not surprising that skeletal defects should commonly accompany the disease. Some of the most common and the most remarkable lesions associated with neurofibromatosis are those affecting the skeletal system.

OSSEOUS LESIONS ASSOCIATED WITH NEUROFIBROMATOSIS

Brooks and Lehman[6] classified the bony changes of neurofibromatosis under three general headings, as follows: (1) scoliosis; (2) abnormalities of growth of individual bones; (3) irregularity of outline of bones, ranging from central or subperiosteal cysts to pedunculated subperiosteal tumors.

LESIONS OF THE SKULL

The bones of the skull are commonly involved in this disease. Pfeiffer,[7] Rosendahl,[8] Farberov,[9] LeWald,[10] Wheeler,[11] Moore[12] and

4. Masson, P.: Experimental and Spontaneous Schwannomas, Am. J. Path. **8**:367, 1932.

5. (*a*) Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, p. 974. (*b*) Penfield, W., and Young, A. W.: The Nature of von Recklinghausen's Disease and the Tumors Associated with It, Arch. Neurol. & Psychiat. **23**:320 (Feb.) 1930.

6. Brooks, B., and Lehman, E. P.: The Bone Changes in Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. **38**:587, 1924. Lehman, E. P.: Recklinghausen's Neurofibromatosis and the Skeleton, Arch. Dermat. & Syph. **14**:178 (Aug.) 1926.

7. Pfeiffer, R. L.: Roentgenography of Exophthalmos with Note on Roentgen Ray in Ophthalmology, Am. J. Ophth. **26**:724, 1943.

8. Rosendahl, T.: Some Cranial Changes in von Recklinghausen's Neurofibromatosis, Acta radiol. **19**:373, 1938.

9. Farberov, B. J.: Röntgenologisches Schädelbild bei Neurofibromatosis Recklinghausen, Ztschr. f. Augenh. **89**:81, 1936.

10. LeWald, L. T.: Congenital Absence of the Superior Orbital Wall Associated with Pulsating Exophthalmos: Report of Four Cases, Am. J. Roentgenol. **30**:756, 1933.

Uhlmann and Grossman,[2] to mention a few, have reported lesions involving the skull. Bulging of circumscribed areas, peculiar vascular designs, enlargement of the sella, enlargement of the orbit and of the optic canal, various types of gross asymmetry, subperiosteal cysts and "bony atrophy and erosions" are some of the most commonly mentioned defects of the skull. Bony defects could be due to destruction of bone by neurofibroma, or they could be congenital defects. It is probable that maldevelopment of bone does occur and that bone is eroded or atrophied because it is involved with tumor. Moore[13] expressed the belief that these lesions of bone are not due to invasion or erosion because these defects are frequently remote from the tumors. This fact is well illustrated in the case of neurofibromatosis with defect in the orbital wall, inasmuch as there is no orbital tumor present in some instances.

DEFECTS IN THE WALL OF THE ORBIT

Defects in the wall of the orbit, permitting free communication between the intracranial cavity and the orbit, are not often mentioned in the literature, but we have encountered 5 cases in a ten year period which would lead us to believe that the syndrome is not as rare as might be inferred from the paucity of reports concerning it. LeWald has shown that unrecognized orbital defects were present in published cases of neurofibromatosis. He collected from the literature several cases of pulsating exophthalmos which was not recognized as being due to a defect of the orbital wall, although in reproductions of roentgenograms accompanying the reports it was possible for LeWald to determine that such defects were present. It is perhaps significant that only a few observers have published cases of orbital defects, although some of these observers reported several cases of neurofibromatosis, a fact which may indicate that these lesions are recognized, as a rule, only by those already familiar with them.

In all 7 cases of neurofibromatosis of the orbit presented by Pfeiffer marked deformities of the bony orbit were revealed roentgenographically. In 5 of the 7 cases a deformity of the optic foramen existed, and in 1 case the optic canal was entirely absent. In 2 of Pfeiffer's[7] cases extensive defects were present in the orbital walls, permitting direct communication of the orbit with the intracranial cavity. Rosendahl[8] reported 8 cases of neurofibromatosis associated with changes in cranial bones. In 1 of these cases there was typical roentgeno-

11. Wheeler, J. M.: Pulsation of the Eyeball Associated with Defects in the Wall of the Orbit, Bull. Neurol. Inst. New York 5:476, 1936.

12. Moore, R. F.: Diffuse Neurofibromatosis with Proptosis, Brit. J. Ophth. 15:272, 1931.

13. Moore, B. G.: Some Orthopedic Relationships of Neurofibromatosis, J. Bone & Joint Surg. 23:109, 1941.

graphic evidence of absence of the roof of the orbit and in another
a defect in the lateral wall of the orbit. Rockliffe and Parsons [14]
reported a case of plexiform neurofibroma of the orbit in which post-
mortem examination showed that the whole orbital plate of the frontal
bone, the lesser and greater wings of the sphenoid bone and the lacrimal
plate of the ethmoid bone were missing. Farberov [9] reported 3 cases
and LeWald [10] 4 cases with definite defects in the walls of the orbit.
LeWald was the first to point out that this combination of neuro-
fibromatosis and defect in the orbital roof is congenital and is not due
to erosion or compression by the growth of the tumor, as other authors
had assumed it to be. Wheeler [11] reported 5 similar cases (2 of these
cases had previously been reported by LeWald) ; A. E. Moore [15] reported
2 cases, and R. F. Moore,[12] van der Hoeve [16] and Avisonis [17] each
1 case, as did Heublein, Pendergrass and Widmann.[18]

<div align="center">REPORT OF CASES</div>

Because of the relative rarity with which these cases have been
reported and because, as has been mentioned previously, it would appear
that this syndrome is usually not recognized when seen, we feel that
5 cases seen at the University of Minnesota Hospitals in the last
ten years should be reported. In all these instances a typical picture of
the syndrome was presented, and perhaps the cases should have been
readily recognized; but, as will be seen, some were not recognized immed-
iately because of unfamiliarity with this feature of neurofibromatosis.

CASE 1.—R. N., a 20 month old white boy, was first seen at the University
Hospitals Dec. 6, 1934. The history of birth revealed nothing unusual. At the time
of his admission there was a history of protrusion of the eyeballs, most pronounced
on the left, which was first noticed three days after birth. There was a serous
discharge from the left eye. At the age of 4 weeks a definite exophthalmos of the
left eye had developed.

Physical examination revealed that the child was fairly well nourished. There
was asymmetry of the skull with prominent parietal bosses. The left parietal area
showed more protuberance than the right and seemed to bulge about 1 cm. There
was definite exophthalmos on the left, and the left pupil was irregular and some-
what larger than the right. The left orbit seemed enlarged on palpation. Tension

14. Rockliffe and Parsons, H.: Plexiform Neuroma of the Orbit, Tr. Path.
Soc. London **55**:27, 1904.

15. Moore, A. E.: Neurofibromatosis Associated with Proptosis and Defect
of the Orbital Wall, Australian & New Zealand J. Surg. **5**:314, 1936.

16. van der Hoeve, J.: Doyne Memorial Lecture: Eye Symptoms in Phakoma-
tosis, Tr. Ophth. Soc. U. Kingdom **52**:38, 1932.

17. Avisonis, P.: Zur Frage über den Zusammenhang der einseitigen Elephanti-
asis des Oberlides mit Erweiterung der Sella turcica, Ztschr. f. Augenh. **63**:
235, 1927.

18. Heublein, G. W.; Pendergrass, E. P., and Widmann, B. P.: Roentgeno-
graphic Findings in the Neurocutaneous Syndromes, Radiology **35**:701, 1940.

of the globes was equal on the two sides, and there was no pulsation or bruit over the eye. There were typical café au lait spots over the buttocks and the abdomen. The remainder of the examination revealed no abnormality.

Roentgenographic examination showed definite enlargement of the left orbit, and the wing of the left sphenoid bone was elevated. Absence of the roof of the orbit was not recognized in the roentgenograms made at this time. A review of the roentgenograms shows that the sella was enlarged, but this was not reported at the time of the original examination. The results of laboratory tests were all within normal limits. It was suggested by a consultant that Recklinghausen's disease with a congenital anomaly was the cause of the child's condition. But this diagnosis was apparently not seriously considered by those directly in charge of the patient, for a course of high voltage roentgen therapy was given, on the assump-

Fig. 1 (case 1).—Exophthalmos with downward and forward displacement of the eye. The left frontotemporal region is protuberant.

tion that the underlying condition was a retrobulbar tumor. This treatment, of course, resulted in no improvement.

The patient was then seen in the outpatient department at frequent intervals for the next several years; on Aug. 17, 1939 a neurosurgical consultant again saw the patient and expressed the belief that the underlying disease was probably neurofibroma associated with a defective orbital roof. For this reason, a left transfrontal craniotomy was performed by one of the junior staff, who failed to recognize an absence of the orbital roof; instead it was thought that an angioma had been found and that this had produced the exophthalmos by extension into the orbit (fig. 1).

Shortly thereafter an encephalogram was made, which showed the tentorium cerebelli to be unusually high, indicating a large cerebellum and posterior fossa. There was slight dilatation of the left lateral ventricle. At this time deformity of the skull was again demonstrated in the roentgenograms and was reported as a

"large left middle fossa, erosion of the wing of the sphenoid bone on the left and enlargement of the left orbit." (A review of these roentgenograms [fig. 2] reveals the typical appearance of absence of the orbital roof, although this was not recognized at the time.)

In June 1941 the patient was again admitted to the hospital, with a history of vomiting, headaches, dizziness and weakness, all of which had been present for one year. These symptoms had progressed to complete disability and prostration. Examination at this time revealed a pulsating, but not expansile, proptosis of the left globe, with neither bruit nor thrill. The eyegrounds were normal. There was bulging of the skull over the left frontotemporal region, and a violent nystagmus to the left occurred when the head was turned in that direction. Evidence of a mild degree of increased intracranial pressure was demonstrated roentgenographically. The child improved under conservative management and was discharged from the hospital.

In May 1942 the child was again admitted to the hospital, and another exploration of the cranial cavity was undertaken by reopening the former transfrontal craniotomy area, with the idea that a retrobulbar tumor, if present, could be

Fig. 2 (case 1).—Enlarged left orbit with absence of its roof, as indicated by absence of the orbital fissures and optic foramen. Anchoring wires are placed in the reconstructed roof of the orbit.

resected or that absence of the roof of the orbit might be repaired if it were found. A plastic reconstruction of the defect in the orbital roof was made with a Lucite plate and a piece of bone taken from the edge of the defect in the skull. These were fastened medially to the remnants of a small shelf of the orbital roof, most of it consisting of cribriform plate, and laterally they were anchored to the skull with silver wire. Thus, a fairly satisfactory roof was made for at least the anterior portion of the defect in the orbital roof. The postoperative course was rather stormy; but the child recovered, and the exophthalmos seemed definitely improved.

The child's last admission was on July 25, 1943. The history in the interval was one of gradual improvement for approximately twelve months after the operation, but two months previous to his final admission there developed severe occipital headaches, anorexia, weakness, fatigue and vertigo. Examination revealed irregularity of the left pupil with gross nystagmus of the right eye. Typical café au lait spots were again noted, not only on the trunk but on all extremities. There were no cutaneous nodules. There was weakness of the extremities on the right side.

The superficial abdominal reflexes were decreased on the right, and the cremasteric reflexes were absent. The knee jerk was absent and the ankle jerk diminished on the right side. The course of the illness was progressively downhill, and the child died Aug. 8, 1943.

Postmortem examination of the base of the brain revealed slight enlargement of the left cerebral hemisphere with a slight displacement of the optic system. The inferior surface of the cerebellum was covered with a gelatinous tumor, measuring 6 by 5 cm. The medulla was enlarged to about twice its normal size, and its posterior surface was incorporated in the gelatinous mass. Midsagittal section revealed a large astrocytoma of the medulla, about 4 by 3 cm. It partially filled the fourth ventricle and invaded the cerebellum (fig. 3). Unfortunately, the defects in the skull were not described in the autopsy protocol.

Comment.—Several interesting features are illustrated in this case. The exophthalmos was first noticed three days after birth; this in itself
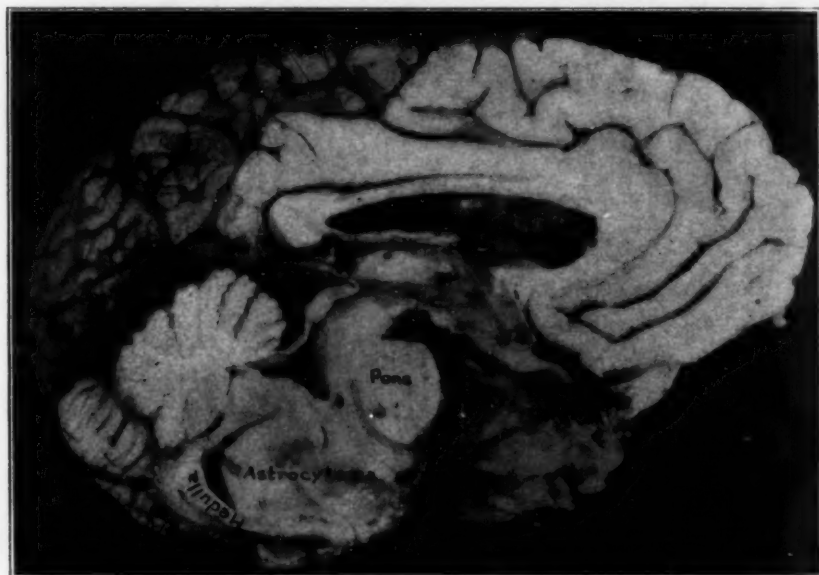
Fig. 3 (case 1).—Astrocytoma of the cerebellum.

would be a strong indication that some congenital anomaly was causing the condition. Temporal or parietal bossing has been reported repeatedly as one of the common changes in the skull associated with neurofibromatosis.[19] This was also noted in 4 of the 5 cases we observed, the roentgenograms showing bulging in the temporal region on the side of the tumor.

The importance of irregularity of the pupil, as demonstrated here, was emphasized by Davis,[20] who showed that it may be an important

19. Cooper, L.: Plexiform Neuroma of Upper Lid and Temporal Region, Tr. Ophth. Soc. U. Kingdom **26**:136, 1906. Rosendahl.[8] Moore.[12]

20. Davis, F. A.: Primary Tumors of the Optic Nerve (a Phenomenon of von Recklinghausen's Disease), Arch. Ophth. **23**:735 (April) 1940.

aid in the early diagnosis of the condition, especially if there is involvement of the optic nerve. He presented 2 cases with progressive irregularity of the pupil due to neurofibromatosis associated with glioma of the optic nerve. In 1 of his cases the signs were minimal, and even post mortem only microscopic infiltration of the optic nerve was found.

At the first operation in this, our first, case the presence of a vascular anomaly was reported. While this was an erroneous interpretation, such anomalies occasionally accompany neurofibromatosis. Rosendahl[8] reported such a case in which an abnormal vascular design in the skull was shown roentgenographically. Hydrocephalus is rather commonly associated with neurofibromatosis, although in this case it was probably due to the neoplasm in the posterior fossa. Of the 5 cases in this series, roentgenographic evidence of increased intracranial pressure was present in 3, and in the only case in which an encephalographic examination was made hydrocephalus was demonstrated (case 1). The only cases in which no evidence of increased intracranial pressure was shown were those of the 2 adults. Zentmayer[21] presented a case of neurofibromatosis with hydrocephalus.

Other types of tumors, both of the brain and of the body in general, are frequently found in association with neurofibromatosis, as was true in this case. As Hosoi[22] pointed out, these growths frequently represent malignant change in one of the neurofibromas, since approximately 13 per cent of neurofibromas undergo malignant change. But, in addition to these malignant degenerations, tumors of other types, having no direct relation to the neurofibromas, are commonly seen. Davis reported 2 cases of neurofibromatosis, 1 of which was very similar to this case. The case was one of a 4 year old child who was operated on for glioma of the optic nerve and who died four years later with an astrocytoma of the temporal lobe on the same side. Rosendahl[8] emphasized the frequency with which gliomas and meningiomas are found associated with neurofibromatosis and presented 2 cases associated with oligodendroglioma of the optic nerve.

The café au lait spots which were present should, of course, have immediately established the diagnosis of neurofibromatosis in this child.

Surgical treatment, if it becomes necessary for relief of the exophthalmos, should consist of reconstruction of the roof of the orbit. Enucleations have been done either on account of an erroneous diagnosis or for relief of severe exophthalmos. In other cases a retrobulbar neurofibroma has been removed by the Krönlein operation. In the latter procedure, at least the globe is not sacrificed; and if a large amount

21. Zentmayer, W.: A Case of Plexiform Neurofibroma Involving the Orbit, Tr. Am. Ophth. Soc. **13**:205, 1912.

22. Hosoi, K.: Multiple Neurofibromatosis (von Recklinghausen's Disease), Arch. Surg. **22**:258 (Feb.) 1931.

of tumor tissue is present and removed the exophthalmos may be improved. But defects in the roof of the orbit which may be contributory to the exophthalmos, or even the entire cause of it, are not affected by this operation. Thus, since the exophthalmos is due in large part to encroachment on the intraorbital contents by cerebral herniation, reconstruction of the defect in the orbital roof through a transfrontal craniotomy would appear to be the proper surgical procedure. Dandy [23] reported 1 case in which this was done, a portion of the skull from the edge of the craniotomy area being used to repair the defect. The result was very satisfactory. In addition to reconstruction of the roof, tumors within the orbit can be exposed and removed by this approach. We used this method in the present case, with some
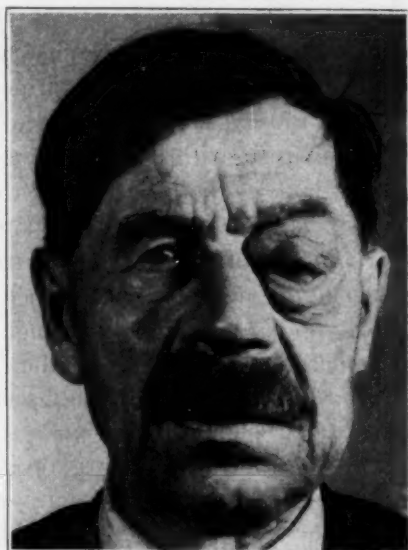
Fig. 4 (case 2).—Proptosis of the left eye due to neurofibromatosis. The eye is displaced downward and forward.

regression in the exophthalmos, but in retrospect it is evident that the cerebral herniation was acting as a decompression in this case because of increased intracranial pressure, which, in turn, was due to a tumor of the cerebellum.

CASE 2.—C. K., a white man aged 63, was first seen in the outpatient department of the University Hospitals in March 1936. At this time he gave a history of pain and increased bulging of his left eye for one year. He had had mild protrusion and poor vision in this eye since childhood, but he attributed the condition to an injury received early in life. However, the exophthalmos had become much worse during the last year.

---

23. Dandy, W. E.: An Operative Treatment for Certain Cases of Meningocele (or Encephalocele) into the Orbit, Arch. Ophth. **2**:123 (Aug.) 1929.

Examination revealed exophthalmos on the left side, with tenderness on pressure over the left globe and around the left orbital rim. The exophthalmometer measurements were 28 mm. for the left eye and 18 mm. for the right eye (fig. 4). The pupil of the involved eye was miotic, reacted to light and in accommodation and dilated with cocaine. Fundoscopic examination revealed no abnormalities. Visual acuity was reported as follows: Distant vision was 20/400 in the right eye and 20/40 in the left eye; near vision was 0 in each eye. Near vision in the left eye could be corrected to 14/20 with glasses, but that in the right eye could not be improved with glasses. The visual defect in the apparently uninvolved (right) eye was thought to be congenital amblyopia.

On the orbital margin of the left malar bone there was a movable firm mass about 1 cm. in diameter, which on biopsy was found to be a fibroma directly connected with a nerve. There were prominent kyphosis of the lower thoracic and upper lumbar portions of the spine and a bony deformity of the right foot, both

Fig. 5 (case 2).—Café au lait spots over the trunk.

of which the patient attributed to a fall sustained many years before; but, in reality, they no doubt were lesions of neurofibromatosis. There were café au lait spots over the trunk (fig. 5). The results of laboratory tests, except for roentgenographic examinations, were normal. Roentgenographic examination of the skull showed an increase in density of the left orbit, with an increase in diameter of this orbit. There was a definite defect in the roof of the orbit, demonstrated by the absence of normal markings. The sella was moderately enlarged (fig. 6).

In June 1943 a portion of redundant tissue was removed from the left lower lid and on microscopic examination was found to be neurofibroma. The roentgenographic changes in the skull were the same as those observed on previous examination.

Additional physical abnormalities noted were paralysis of the seventh and twelfth cranial nerves on the right side. It was advised that nothing be done at this time because of the extremely poor vision in the right eye. However, plastic

repair of the roof of the left orbit was contemplated if the exophthalmos progressed. The patient has, however, been observed periodically, and in January 1945 there was still no demonstrable progression.

Comment.—The bony abnormalities found in this case were sufficient to indicate the true condition, but the diagnosis was confirmed by biopsy. Kyphosis has repeatedly been mentioned as one of the most common bony deformities associated with neurofibromatosis. Brooks and Lehman [6] were so impressed with its frequency and importance that they made it the basis of one of the general groups in their
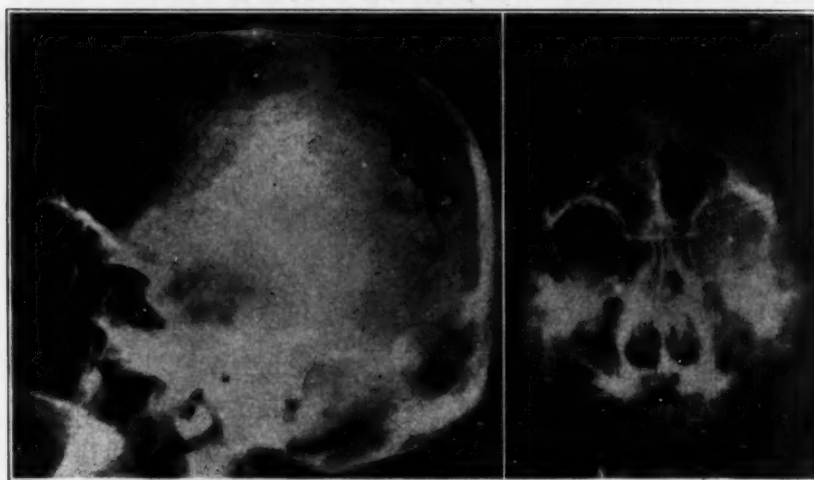
Fig. 6 (case 2).—Increased density in the wall of the left orbit. Absence of the roof is demonstrated by absence of normal markings within the orbit.

classification of these bony changes. Deformity of the long bones is also commonly seen.

A neurofibroma was found on the orbital margin of the malar bone in this case. In most of the cases reviewed a similar neurofibroma was present near the bony deformity, but not necessarily intimately connected with it. Thus, in the present case this tumor may be the only one in the area, and a retrobulbar tumor need not be present to produce the exophthalmos. Moore [13] showed that this situation holds good but pointed out that there seems to be a segmental relationship between the neurofibroma and the bony deformity. He stated the belief that this proves there is a definite etiologic relationship between the two and that it disproves the contention of Brooks and Lehman [6] that the orbital defect is due to invasion of bone by the growth of the tumor.

A consideration of possible therapeutic procedures is of interest in this case. Because of extremely poor vision in the right eye, an enucleation would leave the patient blind; and a retrobulbar exploration

would probably be fruitless, for there is no evidence that a retrobulbar tumor is present. Certainly, the only plausible attack, if it should become necessary to arrest the course of progressive exophthalmos, would be transfrontal craniotomy with reconstruction of the orbital roof.

CASE 3.—W. U., a 7 month old white boy, was first seen at the University Hospitals in September 1936. At this time the parents stated that the child had exophthalmos at birth and that the condition had progressed rather rapidly since.

Fig. 7 (case 3).—Iris adherent to the cornea, with obliteration of the filtration angle.

Fig. 8 (case 3).—Protrusion of the left frontotemporal region. The right eye has been enucleated for buphthalmos.

The history of birth was normal. There were two other children in the family; they were in excellent health and apparently had none of the stigmas of neurofibromatosis.

Physical examination revealed exophthalmos of the left eye, together with greatly increased intraocular tension, deep anterior chamber, smoky cornea and sluggish reaction of the pupil to light. There were two small pigmented areas

on the right flank and a small hemagioma over the left nipple. Roentgenographic examination of the skull revealed that the anterior fontanel was somewhat wider than normal for a child of this age. The left orbit was larger than the right. In November 1936 trephine opening was made in the left globe to relieve the buphthalmos, and this was repeated one month later because of the recurrence of high tension. The abnormal tension returned two weeks after the second trephine opening was made.

In March 1938 the child was again admitted to the University Hospitals because of rapid increase in exophthalmos during the preceding month. This followed a fall, at which time the child hit his left eye.

The left eye was enucleated at this time; unfortunately, however, no mention was made of the condition of the orbital wall. Examination of the enucleated eye revealed it to be greatly enlarged but otherwise grossly normal. Microscopic examination revealed that the iris was adherent to the periphery of the cornea, with obliteration of the filtration angle (fig. 7).

In September 1942 the child was again seen, and at this time café au lait spots were noted on the abdomen and arms. According to the mother, these
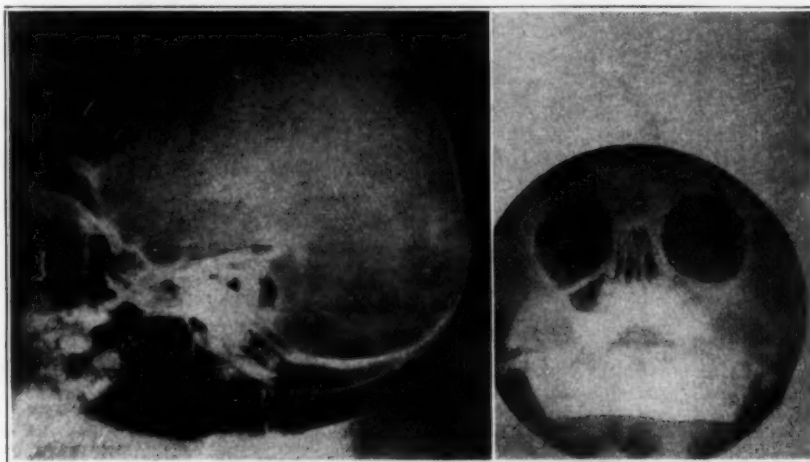
Fig. 9 (case 3).—Large left orbit with elevation of the roof and absence of the posterior part of the roof.

spots had developed since the previous hospitalization. Roentgenographic examination of the skull at this time showed a rather large head with widening of the suture lines (fig. 8). The sella was enlarged, and the whole appearance of the skull suggested slight hydrocephalus. The left orbit was definitely larger than the right, and there was absence of the greater and lesser wings of the sphenoid bone on the left side. The roof of the orbit was high and short, and the posterior portion was absent (fig. 9). There was also bulging of the temporal bone on the side of the orbital defect.

Comment. — Congenital glaucoma and buphthalmos have been reported to be associated with neurofibromatosis. Anderson[24] collected 33 cases with this association from the literature. In 32 of these

24. Anderson, J. R.: Hydrophthalmia or Congenital Glaucoma, London, Cambridge University Press, 1939, p. 166.

cases the glaucoma was associated with facial neurofibromatosis and in 1 case with uveal neurofibromatosis only. In all these cases the condition was unilateral. The author explains the hydrophthalmos on the basis of iris tissue filling the filtration angle. In most of these cases the root of the iris is adherent to the periphery of the cornea. Microscopic examination of the eye in case 3 showed this to be true. In this case there were other characteristic features of neurofibromatosis—pigmentation, hydrocephalus and temporal bossing.

CASE 4.—J. W., a 16 month old white girl, was first seen in the University Hospitals in July 1944, with protrusion of the left eye and a swollen left cheek,
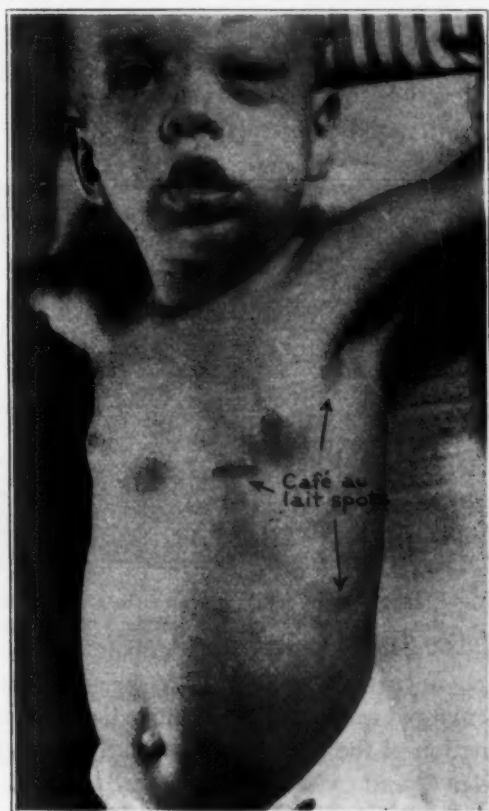
Fig. 10 (case 4).—Café au lait spots over the trunk; exophthalmos of the left eye; neurofibromatosis about the left eye and over the left side of the face.

which was present at birth and had not progressed since that time. There was no associated pain, but a serous nasal discharge and a mucopurulent discharge from the left eye were present. The child was the first born of a 22 year old mother. Pregnancy had been uneventful, and delivery was spontaneous after eight hours of labor.

Physical examination revealed that the circumference of the head was 48 cm., with the anterior fontanel open 1 cm. and pronounced bossing of the left temporal area. There was nonpulsating exophthalmos on the left side, with con-

spicuous edema of the lids and injection of the conjunctiva. Auscultation revealed no bruit. There were edema of the buccal mucous membrane on the left side and a high arched plate. Café au lait spots occurred over the trunk (fig. 10). Roentgenographic examination demonstrated enlargement of the skull and the left orbit with blurring of detail of the bony wall, although structures corresponding to the greater and lesser wings of the sphenoid bone could be seen (fig. 11). There was a definite bulge in the left temporal region, and the sella was somewhat unusual in that there were two depressions: one anterior to the other, the anterior depression being in the usual position of the tuberculum sellae. The skull was rather large, suggesting the possibility of slight hydrocephalus.

Comment.—In this case there were fewer signs pointing to a diagnosis of neurofibromatosis than in any of the other cases in this series. Evidence of hydrocephalus was present, as in 2 of the other cases. The unusual defect in the sella is an interesting feature. There are no reports in the literature of a similar defect associated with neurofibromatosis, but various other sellar abnormalities have been described.
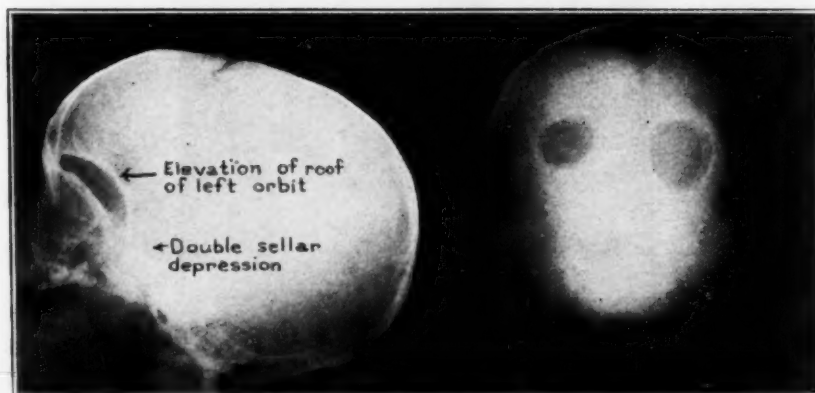
Fig. 11 (case 4).—Enlarged left orbit; partial absence of the roof of the left orbit and elevation of the remaining portion; double sellar depression.

Vogt had 2 cases of neurofibromatosis associated with elephantiasis of the eyelid and enlarged sella and stated the belief that this elephantiasis was due to dysfunction of the pituitary gland. Subsequently, LeWald,[10] Farberov,[9] Wheeler[11] and Avisonis[17] have all shown that defects of the sella are rather common with neurofibromatosis and that they do not indicate any disease of the pituitary gland. In reviewing the roentgenograms in our 5 cases, it was found that all of them showed an enlarged sella.

The only definite evidence of neurofibromatosis in case 4, in addition to the orbital change, was the typical café au lait spots. It should be emphasized that multiple cutaneous tumors are not necessary to make a diagnosis of neurofibromatosis. Penfield and Young[5b] and Preiser and Davenport[1] mentioned that occasionally pigmented spots are the only evidence of the disease throughout life in certain members

of a family, while other members may have the more typical tumors. To this type of disease picture they have applied the term abortive, or incomplete. Rosendahl[8] and LeWald[10] made the diagnosis of neurofibromatosis on the basis of a combination of lesions of bone and typical pigmentary changes. Davis[20] made a diagnosis of neurofibromatosis in 5 reported cases without the aid of cutaneous tumors. In all the cases there was a tumor of the optic nerve; in 1 there were changes in the bones of the leg; in 1 multiple intracranial tumors, and in all typical café au lait spots. In 4 of the cases a positive hereditary history was obtained. Davis[20] emphasized the importance of these
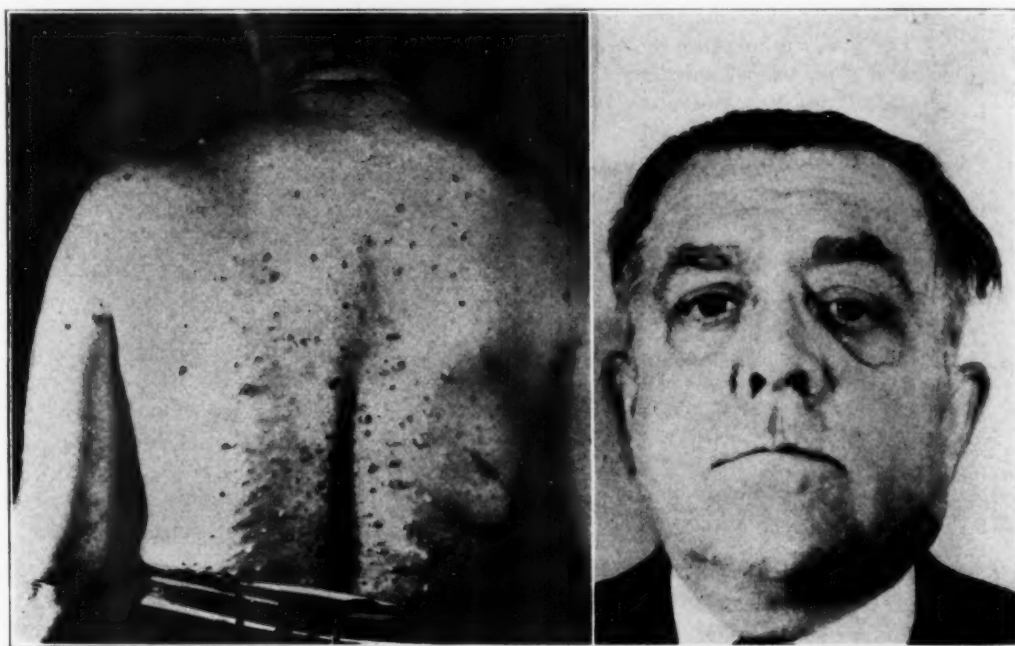
Fig. 12 (case 5).—Cutaneous neurofibromas; unilateral pulsating exophthalmos.

pigmentary changes in making a diagnosis and mentioned that they may be the only positive evidence.

CASE 5.—W. S., a 53 year old white man, was seen in consultation in May 1944 but was not admitted to the hospital. At that time he complained of pulsating exophthalmos. Although this exophthalmos had been present for at least fifteen years, he had never seen a physician about it until February 1944, when he was referred to an internist by an optometrist to whom he had gone for a routine refraction. The internist referred the patient to an ophthalmologist, who made the diagnosis of a retrobulbar tumor but had a roentgenographic examination made of the skull. This revealed a typical picture of absence of the orbital roof, which was recognized by the roentgenologist as an indication of the presence of neurofibromatosis. The patient then came to the neurosurgical service of the University Hospitals for an opinion regarding repair of this defect.

The patient had numerous small nodules scattered over his body; these had been present as long as he could remember. He wore glasses but stated that he did not believe his vision had become any worse during the last several years. There was no family history of neurofibromatosis.

Physical examination revealed a well developed, well nourished white man with pulsating exophthalmos on the left side (fig. 12). No bruit could be heard. The exophthalmos was measured as 24 mm. on the right side and 29 mm. on the left. Visual acuity without correction was 20/50 in the right eye and 20/355 in the left eye, but with lenses it was brought up to 20/20 in each eye. The left eye, in addition to its protrusion, was displaced downward. The pupils were equal and regular and reacted to light and in accommodation. Fundoscopic examination revealed no abnormalities. A small tumor was palpable in the lower eyelid. It was discrete, moderately firm and approximately 7 to 8 mm. in diameter. Extraocular movements were normal.

There was prominence of the temporal area on the left, and a bony defect was palpable just behind the lateral side of the rim of the left orbit. This area seemed to be depressed about 1 cm. below the level of the surrounding bone.
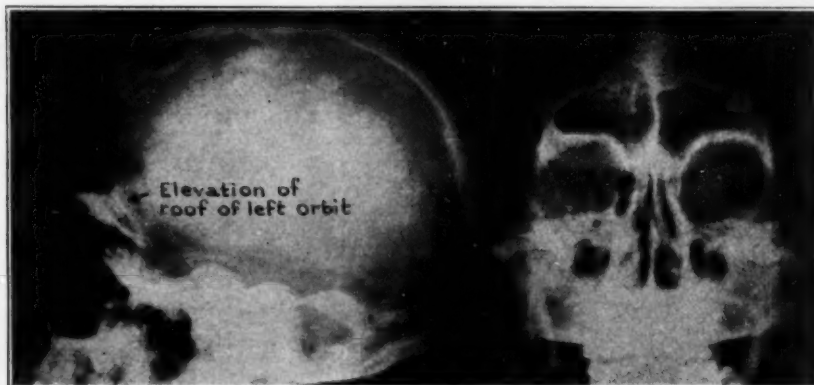
Fig. 13 (case 5).—Large left orbit with partial absence of the roof and elevation of the remaining portion.

A bony defect was palpable at the angle of the mandible on the left. There was no scoliosis, and no other bony abnormalities could be found on physical examination.

The skin was covered with numerous small, soft tumors; many of them were pedunculated and a few showed pigmentation, varying from coffee color to deep purple. These tumors varied in size from 1 mm. to 7.5 cm. in diameter. Over the left scapula there were two small café au lait spots, about 3 cm. in diameter.

Roentgenographic examination revealed definite enlargement of the left orbit with obliteration of the normal orbital detail (fig. 13). There was increased prominence of the left temporal bone, and the sella was enlarged. There were cysts in the left malar bone and in the angle of the mandible on the left.

Comment.—The patient was scarcely aware of any abnormality in the left eye and certainly was not disturbed by it until the first physician consulted suggested that it might be a serious lesion, even a retrobulbar sarcoma being considered. The patient was reassured that it was a benign, and probably nonprogressive, lesion and that no treatment was

necessary. When he was last seen, in January 1945, there had been no progression.

GENERAL COMMENT

The exophthalmos present in these cases of neurofibromatosis may be due to two factors. There may be a retrobulbar neurofibroma or an associated tumor other than neurofibroma, such as glioma of the optic nerve. However, the chief reason for the exophthalmos in most of these cases is the encroachment on the orbit by the intracranial contents.

In most of these cases a pulsating type of exophthalmos is present. These pulsations are due to transmitted pulsations of the cerebrum. It should be emphasized that the pulsations are not due to expansion of the orbital content, as with arteriocavernous sinus fistula, and there is no associated bruit, as there is with a fistula. Moore [12] operated in 1 such case for arteriovenous fistula before he had recognized this feature of neurofibromatosis. Wheeler [11] pointed out that patients who have a portion of the orbital roof removed for exophthalmic goiter (Naffziger operation) may have pulsations of the orbit for a time but these tend to disappear. In cases of the Schüller-Christian syndrome there may be similar large orbital defects, but there are no pulsations. Wheeler stated the belief that in the case of surgical removal of a portion of the orbital roof this bone is replaced by heavy fibrous tissue, which resists pulsations, and he made postmortem examination in a case of Schüller-Christian syndrome in which the orbital defect was reenforced by a layer of xanthomatous tissue about 3 mm. in thickness. On the other hand, in Avisonis' case of neurofibromatosis with absence of the orbital roof, in which postmortem examination was made, only a thin membrane separated the brain from the orbit. Also, in case 1 of this series, at operation no membrane was found replacing the absent portion of the roof of the orbit. Transmission of cerebral pulsations, then, is obviously the reason for the continued pulsations in this condition.

SUMMARY

Some of the general features of neurofibromatosis are discussed.

A review of the literature reveals that 20 cases of neurofibromatosis with defect in the wall of the orbit have previously been reported.

Five cases of neurofibromatosis with defect in the orbital wall are presented, and some of their typical features are discussed.

University of Minnesota Medical School (14).

Case Reports

EARLY EFFECTS OF PENICILLIN TREATMENT OF DEMENTIA PARALYTICA
A Clinical and Psychologic Study

LIEUTENANT J. EDWARD STERN (MC), U.S.N.R.
AND
LIEUTENANT HELEN M. CAMPBELL (H) W-V(S), U.S.N.R.

The introduction of penicillin has caused a renewed interest in the treatment of early [1] and late [2] syphilis. In this paper an account is given of the course of early dementia paralytica in a man aged 31 who at no time was subjected to any other form of therapy. Treatment with penicillin appeared to produce a remission. Psychologic examinations made before and after treatment confirmed the clinical impression of remission and permitted a roughly quantitative estimate of the degree of improvement. Since serologic reversal is often minimal or absent when penicillin alone is used in the treatment of late syphilis, it is suggested that psychologic examinations, repeated at stated intervals, may provide an early indication for repetition of treatment.

The clinical methods used in this study were the standard physical, neurologic and serologic tests and examination of the cerebrospinal fluid. The psychologic methods utilized were the Wechsler-Bellevue Adult Scale [3] for measurement of intelligence and the Rorschach test. [4] The Wechsler-Bellevue examination provides a standardized method for determining the intelligence quotient and for revealing disorders of mental functioning. The Rorschach test is useful for revealing abnormalities of the personality, chiefly in the area of perception and interpretation of reality.

1. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**:355-357 (Dec.) 1943. Mahoney, J. F.; Arnold, R. C.; Sterner, B. L.; Harris, A., and Zwally, M. R.: Penicillin Treatment of Early Syphilis, J. A. M. A. **126**:63-67 (Sept. 9) 1944. Moore, J. E.; Mahoney, J. F.; Schwartz, W. H.; Sternberg, T. H., and Wood, W. B.: The Treatment of Early Syphilis with Penicillin, ibid. **126**:67-73 (Sept. 9) 1944.

2. Stokes, J. H.; Sternberg, T. H.; Schwartz, W. H.; Mahoney, J. F.; Moore, J. E., and Wood, W. B., Jr.: The Action of Penicillin in Late Syphilis, J. A. M. A. **126**:73-80 (Sept. 9) 1944.

3. Wechsler, D.: The Measurement of Adult Intelligence, ed. 3, Baltimore, Williams & Wilkins Company, 1944.

4. Rorschach, H.: Psychodiagnostik: Methodik und Ergebnisse eines wahrnehmungsdiagnostischen Experiments (Deutenlassen von Zufallsformen), ed. 4, Bern, Hans Huber, 1941. Klopfer, B., and Kelley, D. M.: The Rorschach Technique, New York, World Book Company, 1942.

The patient, a yeoman second class, aged 31, had served in the Navy from 1936 to 1940 and again since Dec. 11, 1942, at which time the serologic reaction of his blood (Kahn) was negative. A review of the past history indicated that he had had no severe injuries or illnesses. He had completed three years of courses in arts and letters in junior college and had gone to work at the age of 23. He had been married for three years. During the period of his hospitalization his wife gave birth to their first child; the serologic reactions (Kahn) of both the mother and the child were negative.

On Sept. 3, 1944, after working in the sun for three hours, the patient felt weak, dazed and confused but did not lose consciousness. He was admitted to the hospital on the following day. He stated that since February 1944 he had been studying very hard, had been unable to sleep properly, suffered from frequent headache and fatigability, was unable to concentrate and did not feel as if he was "on his toes."

The general physical examination revealed nothing abnormal. The neuropsychiatric examination disclosed the following points: The pupils were small, but circular and equal and reacted well to light and in accommodation. The deep reflexes were symmetrically hyperactive. Test phrases were moderately slurred. The stream of speech was halting and confused. Perception and orientation were only fair. Memory was poor and, for recent events, seriously impaired. Despite his education his general knowledge was only fair. He followed directions poorly.

The Kahn and Kolmer reactions of the blood on Sept. 10, 1944, were positive (4 plus). Tests of the cerebrospinal fluid made on the same day showed 141 white blood cells per cubic millimeter, of which 99 per cent were lymphocytes; the total protein value was 115 mg. per hundred cubic centimeters; the reaction for globulin was positive, and the Kahn and Kolmer reactions were both positive (4 plus). Colloidal gold solution was not available. Reexamination of the cerebrospinal fluid on September 20 showed 4 white blood cells per cubic millimeter; the total protein value was 115 mg. per one hundred cubic centimeters; the reaction for globulin was positive; the colloidal gold test showed a typical first zone curve, of 5555543200. The urine was normal. Roentgenographic examination of the chest showed a normal cardiovascular silhouette and a calcified primary complex in the upper lobe and the hilar region of the left lung. The electrocardiogram showed minor variations, including slight notching of the P waves, small Q waves and tall R waves, all in leads II and III, and low voltage of the main deflection in lead IV; but it was considered probably to be within normal limits. The records from serial precordial leads were within normal limits.

The diagnosis was established as dementia paralytica, although no history of primary or of secondary syphilitic lesions could be elicited, and the serologic reactions of the blood had been reported to be negative as recently as twenty-two months before the patient's hospitalization, or fifteen months before the onset of the first symptoms.

On October 3, one month after his entry into the hospital, the patient fell to the ground, had some difficulty in using the right arm and leg but did not lose consciousness. Reexamination disclosed no additional abnormalities and there were no sequelae or residual weaknesses.

On October 4 penicillin became available, and treatment was instituted; 40,000 units was administered intramuscularly every three hours day and night for a period of eight days, making a total of 64 injections, or 2,560,000 units. On October 12 the treatment was completed.

On October 6, during the period of treatment, the patient suffered an episode of loss of consciousness of about five minutes' duration. There was no convulsion; the eyes were turned upward; the breathing was stertorous; the deep reflexes were hyperactive throughout; there was persistent ankle clonus, and the Babinski reflex and other signs indicative of disease of the pyramidal tracts were elicited on the right. There were no sequelae to this attack, and the course of treatment was not interrupted.

The serologic reactions of the blood were as follows:

Date (1944)	Reaction	Test
October 14	4 plus	Kahn
October 18	4 plus	Kolmer
November 2	3 plus	Kahn
	Positive (40 Kahn units)	Quantitative

On November 4 the Kolmer test gave a 4 plus reaction in four tubes. On November 29 examination of the cerebrospinal fluid showed 9 lymphocytes per cubic millimeter; the total protein value was 50 mg. per hundred cubic centimeters; the reaction for globulin was negative; the Kahn and Kolmer reactions were 4 plus; the colloidal gold curve was 5555432100. In brief, there were a distinct improvement in the total protein value and a reversal of the reaction for globulin, without change in the serologic reactions or a definite change in the colloidal gold curve.

Shortly after the completion of the course of penicillin the patient showed definite clinical improvement. Test phrases were well pronounced. The stream of speech was free. Perception, orientation, memory, both for recent and remote events, and knowledge were definitely improved. However, clinical examiners found the patient somewhat withdrawn or preoccupied, not quite normally attentive, leaving them with the vague sense of failure to attain full contact or rapport. Whether this was an expression of irreversible impairment or part of the pre-illness personality is not clear.

Detailed psychologic studies were carried out before and after treatment. With the use of the Wechsler-Bellevue scale, mental examination was made on September 28, before penicillin treatment, and was repeated on October 18 (six days after the last injection), on November 8 (twenty-seven days after the last injection) and on Jan. 11, 1945 (ninety-one days after the last injection). The intelligence quotient before treatment was 102; after treatment the ratings were 120, 128 and 131, on the respective dates.

On the first examination, before treatment, the following functions were found to be retarded: (a) memory for acquired facts, with a fund of general information below that of the patient's educational level, and with forgotten facts in some instances covered up by approximations; (b) immediate auditory memory span, with a limit of 6 digits forward and 4 digits backward; (c) perception of form and structural relations; (d) visual-motor coordination; (e) ability to do new thinking; (f) balanced mental control, with reduction of awareness, autocriticism and judgment.

On the second examination, six days after the last injection, there was improvement in every function, with the level of success indicated by an intelligence quotient of 120. The difficulties already mentioned, however, were still clearly in evidence. There was some rigidity of mind, in that the patient could not reverse a digit series greater than 4 or improve on answers to questions in verbal reasoning tests, though they were recognized by him as unsatisfactory.

Verbal expression was cumbersome, and he had difficulty in thinking of appropriate words.

On the third examination, twenty-seven days after the last injection, the intelligence quotient was 128, and on the fourth examination, ninety-one days after the last injection, it was 131. (There was no essential change in mental ability between the third and the fourth examination; the increase of 3 points in the intelligence quotient was clearly attributable to the effect of practice.)

As just indicated, while part of these successive increases in the quantitative score was attributable to the effect of practice, qualitative changes were distinct and dramatic. Nevertheless, minor qualitative difficulties were still noticeable in fine motor coordination (handwriting), in visual-motor coordination, in memory (as shown by the halting nature of the stream of verbal association and difficulty in recalling the correct word desired) and in impaired flexibility of mind (difficulty in seeing various phases of a problem and in accepting and remembering corrections).

Samples of test responses on the first, second, third and fourth examinations are reproduced.

General Information:

What is a thermometer?

1. Degrees, Fahrenheit.
2. To measure heat and cold.
3. To measure temperature.
4. An instrument to measure temperature.

How far is it from Paris to New York?

1. 3,500 miles.
2. 4,000 miles.
3. 5,000 miles.
4. 3,500 miles.

Who wrote Hamlet?

1. Longfellow.
2. The only one I can think of is Longfellow, but I don't think that is right.
3. Shakespeare.
4. Longfellow.

Who discovered the North Pole?

1. Erickson.
2. Peary.
3. Peary.
4. Peary.

What is the capital of Japan?

1. Kobe.
2. Tokyo.
3. Tokyo.
4. Tokyo.

What does the heart do?

1. Beats; pulses; pulses the blood.
2. Circulates the blood.
3. Circulates the blood.
4. Circulates the blood.

Comprehension:

Why should we keep away from bad company?

1. I'd say bad company breeded trouble. [Explain further] You would naturally be considered bad company and be treated thus by others.
2. It breeds disorder. [Explain further] Birds of a feather flock together. You are judged by the company you keep. This is not the best answer, but it is OK, I guess.
3. You are judged by the company you keep. It has a bad influence on you.
4. We will get in trouble ourselves because we will come to hold the thoughts that breed disorder. We are also judged by the company we keep.

Why does land in the city cost more than land in the country?

1. Because of improvements made by the city from the taxes of the people.
2. Because of constant improvements. [Explain further] Taxes are being constantly levied for streets, sidewalks and parks.
3. Because of the improvements made through the use of taxes levied on the people.
4. Because of the improvements and because it is near the heart of industries.

Why are people who are born deaf usually unable to talk?

1. Sound has never crossed their lips. That doesn't sound right—sound has never crossed their lips.
2. They have never been receptive of speech; so they can't speak it. [Explain further] They can't utter a sound. That's it. They can make noises but can't utter a sound.
3. They haven't perceived sound, so can't utter sound. Or, they can't imitate because they can't hear.
4. They have never been able to perceive sound; so they can't pronounce sound or words.

Rorschach records were obtained on September 28, before penicillin treatment; these were repeated on October 19, on November 27 and on Jan. 11, 1945 (seven days, forty-six days and ninety-one days, respectively, after the last injection).

The first Rorschach record, obtained before treatment, showed a general expansion of the personality, with reduction in mental control. There were excessive spontaneity and imagination; slight resemblances (poor form concepts) were interpreted to a degree greater than normal. There was a preponderance of interpretations of movement (of a total of 38 scorable responses, there were 8 interpretations of human figures in motion, 8 of animal figures in motion and 2 of inanimate objects in motion). This should be contrasted

with the occurrence of 3 interpretations using color (secondary to form) in the concept and 3 interpretations using shading for surface texture (secondary to form) in the concept. This pattern of response to the Rorschach test is almost the reverse of that obtained by Oppenheimer and Speijer [5] in a case of dementia paralytica. The remainder of the interpretations (34 per cent) were pure form concepts, unenlivened by color, shading or movement. Poor memory was exhibited, inasmuch as 12 of 50 interpretations originally given were for-

Data on Cerebrospinal Fluid, Serologic Reactions of Blood and Psychologic Examinations in the Course of Penicillin Treatment in a Case of Dementia Paralytica

Date	Cerebrospinal Fluid						Blood		Psychologic Examination	
	Cells per Cu. Mm.	Total Protein, Mg. per 100 Cc.	Globulin	Kahn Reaction	Kolmer Reaction	Colloidal Gold Curve	Kahn Reaction	Kolmer Reaction	Intelligence Quotient*	Rorschach Record
1944										
Sept. 10	141	115	Positive	4+	4+	Not available	4+	4+	...	
Sept. 20	4	115	Positive	...	...	5555543200	...	...	...	
Sept. 28	...	...	......	...	...	....	...	...	102	Expansion of personality; 50 responses
Oct. 4-12	Treatment: 2,560,000 units of penicillin intramuscularly									
Oct. 14	...	...	......	...	...	....	4+	...	...	
Oct. 18	...	...	......	...	...	....	...	4+	120	
Oct. 19	...	...	......	...	...	....	...	...	...	Constriction of personality; 19 responses
Nov. 2	...	...	......	...	...	....	3+	...	...	
Nov. 4	...	...	......	...	...	....	...	4+	...	
Nov. 8	...	...	......	...	...	....	...	...	128	
Nov. 27	...	...	......	...	...	....	...	...	...	Further constriction of personality; 10 responses
Nov. 29	9	50	Negative	4+	4+	5555432100	...	...	...	
Dec. 12	...	...	......	...	...	....	4+	4+	...	
1945										
Jan. 11	...	...	......	...	...	....	...	...	131	No essential change; 15 responses
Feb. 5-12	Treatment: 2,400,000 units of penicillin intramuscularly									
March 8	13	40	Negative	4+	...	5554321000	...	...	...	

* Wechsler-Bellevue scale.

gotten by the patient on the second, and immediate, exposure of the cards during inquiry. There were no interpretations of deteriorated form quality or of bizarre concepts. The mood was mildly euphoric.

The predominant change from the record obtained before treatment to the subsequent three records, obtained after treatment, was in the direction of increased mental control with notable inhibition and general constriction of the personality. There was a reduction in the total number of interpretations from

5. Oppenheimer, E., and Speijer, N.: Results of Rorschach Test in Case of General Paralysis Before and After Malarial Cure, Psychiat. en neurol. bl. **41**:386-391 (May-June) 1937.

50 before treatment to 19, 10 and 15, respectively, on subsequent examinations after treatment. The fourth record, unfortunately, was influenced by pressure from the examiner, and the additions to the previous 10 interpretations were only reluctantly admitted by the patient. Therefore the examination on November 27, forty-six days after the last injection, is perhaps typical for this patient. There was 1 interpretation per card. Four of these interpretations were of human figures in motion, and these were of superior conception. A reaction to color occurred only on the last card, though its role in the concept was difficult to determine: "The nearest I can come is to say this has the characteristic of one of Dali's pictures." The patient revealed himself as having an introverted, meticulous, obsessive-compulsive, mildly neurotic personality structure. Irreversible organic mental impairment was not disclosed by the Rorschach test, though a functional disorder, in evidence before treatment with penicillin, appeared to be improved after treatment.

In an effort to produce a serologic reversal, the patient was given another course of treatment with penicillin from Feb. 5 to 12, 1945. He received 2,400,000 units. Examination of the cerebrospinal fluid on March 8 showed 13 white blood cells per cubic millimeter; the total protein value was 40 mg. per hundred cubic centimeters; the reaction for globulin was negative; the Kahn reaction was 4 plus, and the colloidal gold curve was 5554321000. As the patient was transferred, further observations could not be carried out.

COMMENT

It is recognized that spontaneous remission and intermission may occur in the course of dementia paralytica. Nevertheless, it appears likely that the general improvement observed in this case is attributable to the use of penicillin. It is further recognized that repetition, familiarity and practice may slightly raise the scores in mental examinations; however, it appears likely that the improvement observed was in excess of what might be expected as a result of these factors alone.

It would be erroneous to leave the impression that the patient is considered wholly recovered. That some irreversible damage has occurred seems likely. Though the evidence is subtle, both in clinical and in formal mental examinations, the impression is obtained of possible residual mental impairment.

It is clear that prolonged observation in cases such as the one reported here is necessary before a reliable evaluation of the results of penicillin therapy of dementia paralytica is to be expected. In the light of current data, improvement and reversal of serologic reactions appear to be unusual in cases of dementia paralytica treated with penicillin alone. Consequently, it is suggested that psychologic testing at intervals of six months to one year may provide an early indication for the resumption or repetition of treatment, before gross clinical symptoms of relapse make themselves evident.

SUMMARY

A case is presented of dementia paralytica occurring in a man aged 31 whose serologic reactions were negative fifteen months before the onset of symptoms.

The treatment consisted of two courses of penicillin; no other form of treatment was utilized.

Improvement was observed in the general condition, in the cell content, in the total protein and globulin values of the cerebrospinal fluid and in the psychologic scores, while none was found in the serologic reactions of the blood or the cerebrospinal fluid.

Subtle evidences of residual mental impairment were persistent.

It is suggested that reexamination at stated intervals, with particular reference to psychologic testing, may provide an early indication for the resumption of treatment.

109-115 Jamaica Avenue, Richmond Hill 18, N. Y.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

THE HUMAN PYRAMIDAL TRACT. A. M. LASSEK, J. Nerv. & Ment. Dis. **99**:22 (Jan.) 1944.

The belief that the human pyramidal tract is composed of fibers originating in the gigantopyramidal cells of the cerebral cortex has developed as the result of a long series of experiments and observations, culminating in the papers of Grunbaum and Sherrington, of Campbell and of Holmes and May, all appearing in the first decade of the present century. After a number of years of study, Lassek concludes that this concept must be questioned in the light of recent anatomic discoveries. Because of the relative ease of exciting movements of the contralateral limbs by the electrical stimulation of area 4, the pyramidal tract fibers theoretically should be composed of large myelinated fibers, since large cells and fibers are more readily stimulated by electrical currents. However, actual fiber counts of the pyramidal tracts reveal that the great majority of the fibers are diminutive (90 per cent being between 1 and 4 microns).

Campbell's reasoning in assigning to the Betz cells the origin of the pyramidal tracts can be criticized as being of a somewhat *post hoc* nature, owing to his acquaintance with the work of Sherrington and Grunbaum. Also, his definition of a Betz cell is faulty, as is his estimate of the number of such cells. In addition, there is a distinct disparity between the estimated number of Betz cells and that of the pyramidal tract fibers.

The experiments of Holmes and May on retrograde degeneration do not account for the fact that small cells do not exhibit typical changes but, instead, often disappear without a trace, so that injury to their axonal fibers would not reveal the fact that the fibers originated from them. The relatively small number of Betz cells (25,000 to 34,000) could not possibly account for the large number of pyramidal tract fibers.

On the other hand, some investigators, using either a stain for myelin sheaths or a silver technic, have found that many small fibers are left intact in the pyramids after removal of area 4. CHODOFF, Langley Field, Va.

THE ANTERIOR CEREBRAL ARTERY IN THE MACAQUE MONKEY (MACACA MULATTA). JAMES B. CAMPBELL and FRANCIS M. FORSTER, J. Nerv. & Ment. Dis. **99**:229 (March) 1944.

In the macaque, the anterior cerebral artery supplies the following structures: the optic chiasm, the paleo-olfactorium, the inferomedial part of the head of the caudate–putamen mass and the anterior part of the medial two thirds of the globus pallidus, as well as the inferior aspect of both limbs of the internal capsule, the anterosuperior portion of the thalamus, the corpus callosum, the cortex of the medial surface of the hemisphere as far back as the parieto-occipital fissure and a cortical strip on the lateral surface. In a number of macaques, injection studies, using crystalline gelatin dissolved in india ink, were carried out at varying times after ligation of the anterior cerebral arteries. When the ligation was carried out at the level of the genu of the corpus callosum, there resulted retardation, under-activity, prehensile difficulty, weakness of the legs and a positive Babinski sign. Occlusion at the level of the confluence of the arteries caused postural changes in addition to those already noted, which were more severe. Occlusion at the origin of the arteries resulted in coma, followed by stupor and, finally, by underactivity. The postural changes, plantar signs and underactivity were all greater than in the

preceding operations. Neuropathologic changes included softening of the corpus callosum and infarction of the cortex of the frontal lobe. Microscopically, there was noted diffuse involvement of cortical cells extending from the frontal to the occipital lobe, particularly in the former; in addition, there were cellular changes in the head of the caudate nucleus, perivascular demyelination of the internal capsules and occasional glial scars in the ventral thalamic nuclei.

The studies indicate that ligation of the anterior cerebral artery is not an innocuous procedure and that the changes are more widespread than would be suspected. The psychomotor phenomena are probably attributable to the lesions of the anterior frontal lobe, cingulate gyrus and thalamus, while involvement of the basal ganglia may account for the postural changes, masklike facies and occasional tremulousness. However, in view of the widespread lesions, particular symptoms cannot be definitely ascribed to lesions of specific areas.

CHODOFF, Langley Field, Va.

Physiology and Biochemistry

EMOTIONAL FACIAL EXPRESSIONS OF CATS IN BULBOCAPNINE CATATONIA. HERMAN DE JONG and ETHEL CHASE, J. Nerv. & Ment. Dis. **98**:478 (Nov.) 1943.

One of the authors (H. de J.) has produced experimental catatonia in animals with bulbocapnine (hydrochlorate or phosphate), the state consisting of catalepsy, resistance to change of position and autonomic phenomena, such as polypnea and salivation. With large doses of the drug, hyperkinesia and abnormal postures are also produced. In addition, the facial and vocal expressions of the intoxicated animals show a series of swiftly changing and characteristic features. These changing expressive attitudes were sketched by one of the authors (E. C.), an artist, under the supervision of the other author. Five cats were studied in this manner after the intramuscular injection of 20 to 40 mg. of bulbocapnine phosphate per kilogram of body weight. Five drawings which typify the gamut of emotional expressions observed in the animals, together with two sketches of patients in catatonic states, are presented. These drawings show that definite changes in facial expression occur, including such intense emotional reactions as crying and howling. The authors conclude that while it is impossible to judge the nature of pathologic emotional states in animals, the facial and vocal expressions observed and recorded in the cats show evidence of such states, occurring either spontaneously or as an inadequate reaction to external circumstances.

CHODOFF, Langley Field, Va.

A REACTION AROUND CEREBRAL VASCULAR LESIONS AND ITS BEARING ON CEREBRAL LOCALIZATION. LELAND B. ALFORD, J. Nerv. & Ment. Dis. **99**:172 (Feb.) 1944.

Alford discusses the discrepancies in attempts at cerebral localization in such conditions as the aphasias and allied syndromes. The failure of anticipated effects to develop from lesions of certain areas, as well as the occurrence of improvement in cases in which the supposed source area was presumably destroyed, has been explained by von Monakow on the basis of diaschisis and by the relearning, or "round-about," psychologic solution of Goldstein. Others have mentioned the possibility of a shift in cerebral dominance occasioned by forced changes in handedness. The usual explanation for phenomena of this type is the assumption of function by other parts of the brain, especially by corresponding areas of the opposite hemisphere. Alford believes the most important factor to be the reactions which occur in the cerebral tissues surrounding the foci of actual destruction in vascular softening.

In support of this theory, the author cites material from Henschen's collection, in which hemiplegia occurred in a number of cases in which the lesion destroyed only a part of the motor cortex or was far distant from any part of the motor tract. A study of 12 cases of homonymous hemiamblyopia due to old vascular lesions demonstrated that there was a general involvement of the optic radiation,

a condition that could be produced not by a direct destructive effect but by a widespread, evenly distributed change.

The nature of the postulated reaction in the normal tissues beyond the limits of the visible lesion is not clear. The author suggests that the cerebral structure has a unique response to injury in the nature of some obscure physicochemical mechanism.

CHODOFF, Langley Field, Va.

THE CLINICAL AND PHYSIOLOGICAL SIGNIFICANCE OF MAYER'S PHALANGEAL REFLEX. L. HALPERN, J. Nerv. & Ment. Dis. **99**:264 (March) 1944.

Absence of Mayer's reflex spontaneous extension and adduction of the thumb produced on maximal passive flexion of the second or third finger at its basal joint has been considered evidence of a lesion of the contralateral pyramidal tract. In refutation of this view, Halpern presents a number of cases of cerebellar disease or chorea in which the reflex was absent. All the cases were characterized by marked hypotonia of the arm in which the phalangeal reflex was absent without any evidence of disease of the pyramidal tract. Thus, absence of the phalangeal reflex does not indicate cortical disease but, instead, occurs only as a result of diminished muscular tone, whether this is due to choreic, cerebellar or pyramidal factors. This explanation accounts for the absence of the reflex with paresis of the median or ulnar nerve, injury to the cervical portion of the cord and certain of the myopathies.

Contralateral increase in the reflex has occasionally been recorded in cases of tumors of the frontal lobe. In cases in which this occurs there are usually also found intensification of Léri's sign and forced grasping. The occurrence of these signs in such cases is explained as evidence of increased muscular tone in the affected limb.

CHODOFF, Langley Field, Va.

A CONTRIBUTION TO THE DIFFERENTIAL DIAGNOSIS OF MYOCLONUS. HERMAN DE JONG and LOUIS JACOBS, J. Nerv. & Ment. Dis. **99**:290 (March) 1944.

Although myoclonus can be readily differentiated from chorea, athetosis, tremor and tic, it is almost impossible to differentiate myoclonus and fibrillation by their external appearance. In the case of a 14 year old boy with adventitious muscular movements this diagnostic problem arose and was studied by the authors, who used mechanograms of the muscular activity, recorded with ink-writers on a kymograph. Twitchings of the affected muscles were produced during and after muscular activity, during sensory stimulation on any part of the body and as a result of emotion. No twitchings were produced by direct stimulation of the muscle or by the intramuscular injection of neostigmine methylsulfate. The twitchings stopped completely during sleep. All these observations, except the first are indicative of myoclonus and are the opposite of what is found with infiltration. Myoclonic movements originate central to the lower motor neuron, while fibrillations probably have their origin in the affected, muscle or at the neuromuscular junction.

CHODOFF, Langley Field, Va.

THE EFFECT OF DESOXYCORTICOSTERONE IN EPILEPSY. ROBERT B. AIRD, J. Nerv. & Ment. Dis. **99**:501 (May) 1944.

In keeping with the work which has been done in the study of convulsive states with the use of various agents known to modify the permeability of the cerebral cortex and the blood-brain barrier, Aird employed desoxycorticosterone, which is known to reduce capillary permeability.

Groups of white mice were tested for susceptibility to convulsions induced with cocaine hydrochloride after each had received 0.02 cc. (0.1 mg.) of desoxycorticosterone acetate intraperitoneally. It was found that protection against the convulsive effect of the cocaine was afforded only for a short time and was not present twenty-four hours after the administration of the substance.

In a group of cats, the convulsive threshold, determined with electrical stimulating and recording technics, was not appreciably altered after the daily administration of 1 mg. of desoxycortiosterene acetate intraperitoneally for four days.

In 2 patients with clinical epilepsy who had previously failed to respond satisfactorily to the usual anticonvulsant measures, a trial of moderate doses of desoxycorticosterone acetate failed to produce beneficial results.

The early protective effect of the substance against cocaine-induced convulsions is probably due to its effect in altering the permeability of the blood-brain barrier. This mechanism is similar to that observed in the use of the supravital dyes, vital red and trypan red, except that the effect of these dyes lasts considerably longer. The hypothesis of McQuarrie and associates that the anticonvulsant effect of desoxycorticosterone is due to its action in causing electrolytic shifts and corresponding alterations in water balance in the central nervous system is not borne out by the failure of the substance to modify the convulsive threshold as determined by electrical stimulation.

CHODOFF, Langley Field, Va.

NEUROPATHOLOGICAL STUDIES IN VITAMIN E DEFICIENT RATS. RICHARD W. HARVEY and JAMES H. PERRYMAN, J. Nerv. & Ment. Dis. **99**:631 (May) 1944.

Harvey and Perryman review the literature on the neuropathologic conditions found in vitamin E-deficient rats. Such changes as paralysis, muscular impairment, tremor and loss of righting reflexes have been observed by other investigators in suckling rats born of vitamin E-deficient mothers, and lesions in the central nervous system and muscular degeneration have been demonstrated.

A group of 106 rats born of vitamin E-deficient mothers was selected for investigation. Half of these received adequate alpha tocopherol and served as controls. Extensive neuropathologic studies of the central nervous system involving the use of several staining methods were carried out. No significant difference between the control group and the vitamin E-deficient rats was observed. The authors suggest that some of the contradictory reports by previous investigators may be due to differences in technic or interpretation.

CHODOFF, Langley Field, Va.

THE CENTRAL NERVOUS SYSTEM AND HEMATOPOIESIS. S. P. LUCIA and H. F. MARASSE, J. Nerv. & Ment. Dis. **99**:734 (May) 1944.

Lucia and Marasse review the literature and undertake a critical analysis of the relation of the central nervous system to hematopoiesis. A number of workers have reported the experimental production of reticulocytosis in animals following lesions of the diencephalic-pituitary region, but the significance of this is questionable, since reticulocytosis in the presence of a normal or an elevated erythrocyte count may not be indicative of erythropoiesis. The evidence for the existence of an erythropoietic center in the diencephalon or of a hematopoietic hormone in the pituitary gland is far from conclusive. A larger amount of experimental evidence in favor of the existence of a leukopoietic center in the central nervous system has been accumulated. Rosenow (1928), working with rabbits, concluded that there is a leukopoietic center in the diencephalic area, and Borchardt (1928) confirmed his results. There have been a number of reports in which the occurrence of polycythemia, anemia or leukocytosis has been attributed to various pathologic conditions of the central nervous system, such as tumor of the pituitary body or the brain, lesions of the midbrain, narcolepsy, epilepsy, encephalitis, intracranial hemorrhage and cerebral concussion, or has followed lumbar puncture or encephalographic and ventriculographic examination. The authors assert that it is impossible to establish a causal relationship between the central nervous system and hematopoiesis on the basis of these reports, many of which are highly theoretic and based on insufficient cases.

Fifty-nine cases of disease of the central nervous system with autopsy were studied with relation to the peripheral erythrocyte count and the cellularity of the bone marrow. No valid instance of polycythemia was found. In no case did qualitative changes in the bone marrow show correlation with lesions of any particular area of the nervous system. The authors conclude that any relationship between the lesions and hematopoiesis is fortuitous.

CHODOFF, Langley Field, Va.

Neuropathology

VARIATIONS OF BLOOD DIASTASE AND GLUCOSE IN DEPRESSION. CHARLES S. ROBERTS, WILLIAM J. TURNER and JAMES H. HUDDLESON, J. Nerv. & Ment. Dis. **99**:250 (March) 1944.

The authors briefly review the literature on the relationship between the psychotic states and the diastase and glucose levels of the blood. They emphasize the usefulness of longitudinal studies involving intraindividual comparisons, rather than comparisons of groups of psychotic patients with groups of normal persons. Serial determinations on each subject relating changes in the levels on a particular day to changes in the patient's emotional state on the same day are required.

A group of depressed patients who were being periodically rated on such items as loudness of voice, speech rate, facial expression of sadness and apathy were subjected coincidentally to determinations of the diastase and glucose contents of the blood. It was found that increases in blood glucose were related to increases in loudness of voice, speech rate and increasing sadness as judged from facial expression, while blood diastase activity was related to decrease in loudness of voice and to increase in apathy. The authors conclude that a relationship may exist between the glucose level and the diastatic activity of the blood and certain symptoms of depression.

CHODOFF, Langley Field, Va.

VERTEBRAL FRACTURES IN METRAZOL THERAPY WITH AND WITHOUT THE USE OF CURARE AS A SUPPLEMENT. NORMAN L. EASTON and JOSEPH SOMMERS, J. Nerv. & Ment. Dis. **99**:256 (March) 1944.

Eight hundred patients with mental disease given metrazol therapy were studied with reference to spinal injuries. Fractures of one or more vertebrae were found in 26.1 per cent of the patients, including 37.2 per cent of the males and 16.8 per cent of the females. The incidence of fractures was higher in the age group under 21, owing presumably to the fact that the spine has not yet reached its full adult strength. In the 209 patients who sustained fracture, 535 vertebral bodies were involved—581 fractures in males, or 2.8 per patient, and 154 fractures in 73 females, or 2.1 per patient. All fractures occurred in the thoracic portion of the spine, involving especially the fourth, fifth and sixth vertebrae. In no case did the fracture involve the pedicles, laminas or processes. It was found that a preexisting osteoporosis doubled the number of fractures, while kyphosis, scoliosis, arthritis, nuclear change or old fractures did not increase the tendency to injury. If fracture did not develop during the first course of metrazol treatment, a vertebral injury was unlikely to occur during subsequent "shock" therapy. In patients examined roentgenographically at varying intervals up to two years after the treatment, no delayed or late vertebral changes were found.

In a series of 275 patients treated with curare before the induction of the metrazol convulsion, there was a striking decrease in the number of vertebral fractures (from 26.1 to 5.8 per cent). There was also a decrease in the degree of compression and the number of vertebrae involved. The authors believe that curare should be used as a supplement whenever metrazol therapy is employed.

CHODOFF, Langley Field, Va.

Psychiatry and Psychopathology

NEUROPATHOLOGICAL AND PSYCHOPATHOLOGICAL IMPLICATIONS OF BILATERAL PRE-
FRONTAL LOBOTOMY. GEORGE W. KISKER, J. Nerv. & Ment. Dis. **99**:1 (Jan.)
1944.

Kisker reviews at some length the historical background and development of
prefrontal lobotomy and discusses the present views on the procedure from the
standpoints of therapeutic implications and experimental psychopathology.

Attempts at surgical treatment of insanity date from the trephination rites of
primitive man, but it was not until 1936 that Moniz and Lima developed, on a
reasoned and scientific basis, a controlled technic for the therapeutic cortical and
subcortical intervention. This followed a considerable amount of experimentation
on functions of the frontal lobe in animals, notably Fulton and Jacobsen's work
on primates, and the observations from a number of clinics on the changes in
personality and behavior in patients following frontal lobectomy for neoplasm. The
observations of Ackerly (1935), Brickner (1936) and Rylander (1939) were of
special importance. Moniz came to believe that certain types of mental disorder
were the result of persisting cell complexes of the frontal regions of the brain,
and he devised various technics for destroying the tissue, in the belief that a
favorable reorganization of behavior would result. Moniz' procedures have been
refined and extended by both European and American surgeons. In this country
the pioneer and major work has been done by Freeman and Watts.

The operation is concerned primarily with the transection of the neural pathways
between the thalamus and the frontal association areas. This is done through
bilateral trephine openings and the insertion of a cutting instrument, which is
swept upward and downward. A variety of postoperative pictures are seen, with a
prevailing tendency toward either depression or euphoria, depending to a large
extent on the preoperative personality organization and to a lesser extent on the
plane of the section. During the postoperative period a number of transitory
phenomena are present. Somatic symptoms include bulemia, a positive Babinski
sign, vesical and rectal incontinence, vesical retention, ataxia, stupor, aphasia and
hemiplegia. Emotional symptoms include emotional flattening, diminished spon-
taneity, lack of attention, loss of judgment, indifference, euphoria, perseveration,
talkativeness, disorientation and *Witzelsucht*. Freeman and Watts believe that
lobotomized patients lose their self-critical power, become more extroverted in
behavior and lose their fear of the future. Worchel and Lyerly (1941) reported
a series of cases in which preoperative and postoperative psychologic examinations
were performed. They found a lack of intellectual change and a heightened post-
operative emotional tone. Strecker, Palmer and Grant found postoperatively in
a group of 5 schizophrenic patients a disappearance of aggressive tendencies and
an increased emotional flexibility but no appreciable intellectual deficiency. In a
review, covering 500 cases, Drake and Hibbard (1942) conclude that the most
suitable patient for lobotomy shows extreme and persistent anxiety and apprehen-
sion. Specifically, the best results have been attained with anxiety and obsessive-
compulsive states, agitated depressions and agitated schizophrenia.

The author reports observations on the behavior of 20 psychotic patients sub-
jected to lobotomy. Especially striking was the rapidity with which signs of
anxiety and tension were relieved and the more or less persistent disorganization
of the time schema. The profound transformation of the personality patterning
was interpreted as a function of affective-emotional restructuralization rather than
as an alteration of intellectual processes. No measurable impairment in intellectual
ability was observed. General behavioral changes were similar to those described
by other investigators except that the favorable prognostic value imputed by other
workers to postoperative dulness and retardation was not found. The postoperative
confusions so often described were considered to consist more specifically of dis-
turbances in time, space and body schemes.

Lobotomy has stimulated interest and curiosity in certain neurodynamic prob-
lems of the human brain, namely, the problems of corticothalamic relations, of

autonomic representation in the cortex, of cerebral localization and of somnolence. Although the ultimate therapeutic value of lobotomy cannot be assessed, the results are pragmatically encouraging. Of the 20 reported cases, there were decided improvement in 35 per cent, slight improvement in 15 per cent and no improvement in 35 per cent. The best results were obtained with agitated depressions.

CHODOFF, Langley Field, Va.

TRAUMATIC PSYCHOSIS: A QUESTIONABLE DISEASE ENTITY. NATHAN MOROS, J. Nerv. & Ment. Dis. **99**:45 (Jan.) 1944.

Moros discusses the problem of whether it is ever justifiable to make a diagnosis of traumatic psychosis when psychotic behavior occurs in conjunction with headache, dizziness, irritability and fatigability following a head injury. Analysis of records from a number of institutions reveal that such a diagnosis is rarely made. The author analyzes 41 cases of hospitalized veterans with a condition diagnosed as traumatic psychosis, pointing out in each case that factors other than trauma were of paramount importance in the genesis of the observed symptoms. In no case were there sufficient data to justify the tracing of the illness entirely to trauma, although in 25 cases it was thought that trauma played a role in precipitating and aggravating a mental illness basically attributable to other causes. The author concludes that the diagnosis of traumatic psychosis as a disease entity is not warranted.

CHODOFF, Langley Field, Va.

HOMOSEXUALITY: A BIOLOGICAL ANOMALY. EDWIN G. WILLIAMS, J. Nerv. & Ment. Dis. **99**:65 (Jan.) 1944.

Williams differentiates between the male who occasionally indulges in homosexual activity as a substitute for heterosexual relations and the one who habitually prefers to assume the feminine role in homosexual intercourse. Men of the latter type are designated as feminine homosexual males. During an incidental investigation it was noted that in 2 homosexual males of this type there was no drop in serum cholinesterase activity following the administration of 1 mg. of neostigmine methylsulfate, while in sexually normal men such a drop was regularly noted. With the manometric method of Rinkel and Pijoan, the serum cholinesterase activity was determined before and after the subcutaneous injection of 1 mg. of neostigmine methylsulfate in a group of men of the feminine homosexual type and in 3 control groups, 2 consisting of sexually normal men and 1 of men of the masculine homosexual type. With few exceptions, there was a definite reduction in cholinesterase activity in the control groups, while none of the 12 men comprising the group of the feminine homosexual type showed any appreciable decrease. The author interprets this observation as indicating a definite biologic difference between the feminine male homosexual group and all others studied.

CHODOFF, Langley Field, Va.

SIGHING AND OTHER FORMS OF HYPERVENTILATION SIMULATING ORGANIC DISEASE. PAUL A. GLIEBE and ALFRED AUERBACK, J. Nerv. & Ment. Dis. **99**:601 (May) 1944.

It has been shown that deep breathing produces dizziness, numbness and tingling of the extremities and may simulate common diseases, such as heart disease, asthma, peptic ulcer, thyrotoxicosis and convulsive disorders. The hyperventilation syndrome usually occurs in the absence of organic disease and is an important mechanism of psychosomatic disease whereby emotional disturbances can produce physiologic and biochemical changes and physical symptoms. In susceptible

subjects the authors have observed the appearance of headache, light headedness, dizziness, faintness, breathlessness, palpitation, numbness and tingling of the face and extremities, weakness, confusion and anxiety in a period varying from a few seconds to twenty minutes. The biochemical basis for the symptoms is the production of alkalosis due to the increased loss of exhaled carbon dioxide.

In testing for symptoms of hyperventilation, the patient breathes in and out deeply until symptoms appear. If none are present at the end of three minutes, the test is discontinued provided that it has been observed that the ventilation was tripled or quadrupled. If the symptoms produced are those of which the patient originally complained, the relationship should be explained to him.

In 4 illustrative cases from a large series, the hyperventilation syndrome was shown to be responsible for symptoms which had previously been diagnosed, respectively, as coronary disease, petit mal, epilepsy and neuralgia. In each of the cases the demonstration of the relationship between overbreathing and the patient's complaints served as an introduction to successful psychotherapy. In addition, the patients were taught to correct improper respiratory habits.

In most of the cases studied there were found such factors as a family history of neurotic tendencies, childhood inadequacy, feelings of frustration or poor marital and sexual adjustments. It was frequently found that if sexual relations were unsatisfactory, both husband and wife would show symptoms of hyperventilation. The condition was found in women three or four times as frequently as in men, and the age group from 20 to 40 was most frequently represented.

In the treatment of the hyperventilation syndrome, psychotherapy is the main weapon. Drug therapy, such as phenobarbital and ammonium chloride in 7.5 grain (4.8 Gm.) doses (for the acidifying effect) is a relatively unimportant adjunct.

The authors believe that the effort syndrome and neurocirculatory asthenia are expressions of hyperventilation.

CHODOFF, Langley Field, Va.

Diseases of the Brain

THE NEUROLOGIC COMPLICATIONS OF HEMOPHILIA. P. M. AGGELER and S. P. LUCIA, J. Nerv. & Ment. Dis. **99**:47. (May) 1944.

The essential defect in coagulation characteristic of hemophilia is a delay in the conversion of prothrombin to thrombin, apparently due to a deficiency of thromboplastin or a thromboplastin-like substance in the plasma. Whether the defect is inherent in the plasma or in the platelets is not clear.

Lesions of the nervous system are not frequent in cases of hemophilia. Aggeler and Lucia, in a review of all known instances of neurologic complications of the disease, were able to find only 45 such cases. Three authentic and several somewhat doubtful cases of hemorrhage into the cerebral hemispheres were found. No instance of hemorrhage into the cerebral ventricles, cerebellum or medulla and only a single case of hemorrhage into the pons was encountered. Hematomyelia as a complication of hemophilia has been reported in 5 cases. Primary subdural and subarachnoid hemorrhage has been reported in several cases verified at autopsy. One probable case of spinal epidural hemorrhage occurring in association with hemophilia has been recorded, while there have been several cases of spinal subdural and subarachnoid hemorrhage. Involvement of the facial, sciatic, femoral, peroneal, median and ulnar nerves has been noted by various observers.

The authors give the histories of 3 new cases in which neurologic complications of hemophilia occurred. In the first case spontaneous cerebral hemorrhage, as well as chronic arachnoiditis resulting from previous subdural and subarachnoid hemorrhages, was found. In the second case there was paralysis of the left femoral nerve, and in the third case, paralysis of the left femoral nerve, in addition to massive hemophiliac pseudotumor of the left ilium.

CHODOFF, Langley Field, Va.

PAPILLEDEMA (CHOKED DISC) AND PAPILLITIS (OPTIC NEURITIS): THEIR DIFFER-
    ENTIAL DIAGNOSIS. FREDERICK C. CORDES and SAMUEL D. AIKEN, J. Nerv. &
    Ment. Dis. **99**:576 (May) 1944.

Papilledema is due to disturbance in the normal pressure relationship of the
circulation on the two sides of the lamina cribrosa and may be due to ocular,
orbital, intracranial or systemic causes. Sudden lowering of the intraocular
pressure, as well as increased intracranial pressure, may produce the picture. Brain
tumor is the most frequent single cause and was found to be associated with
papilledema in 80 per cent of Paton's series of 252 cases. The early appearance
of papilledema is characterized by a swelling of the nerve fiber sheaths in a
limited area of the disk, followed by elevation of the vessels of the disk and
absence of the venous pulse. Later, the disk tissue becomes opaque; the margins
become obliterated, and the typical elevation of the disk appears. Because of the
edema, the disk appears to be twice its normal size. Arteries are contracted
and veins dilated. Exudates and hemorrhagic spots usually appear. After papil-
ledema has existed for a long time, atrophy sets in, although fully developed
choking of the disk can recede without leaving visible evidence. Central vision
remains normal for a long time. There are enlargement of the blindspot and various
forms of perimetric defect. Pathologically, there is edematous swelling of the
nerve fibers, with a rather abrupt termination of the area of edema at the point
where the retinal vessels leave the nerve. There are important changes in the
nerve fibers, ending in degeneration of neural elements.

The term "optic neuritis" designates an inflammation of the optic nerve with
some signs of involvement of the disk. The most important symptom is loss of
central vision. This is usually accompanied with pain in and behind the eye,
especially on movement, lowering of dark adaptation and slow dilatation of the
pupil after the initial contraction when light is thrown on it. The tendency toward
recovery is strong. Ophthalmoscopically, the disk is hyperemic, owing to dilatation
of the capillaries, and there may be an accompanying neuroretinitis. The inflam-
mation is usually unilateral, and the swelling is rarely over 2 D. Perimetric
examination reveals a central scotoma and peripheral contraction. Pathologically,
there are proliferative changes in the interstitial tissues, primarily perivascular,
followed by degeneration of nerve elements with resultant gliosis.

The following points are helpful in the differential diagnosis of the two con-
ditions: (1) Sudden loss of central vision is the most important sign of papillitis;
(2) in papillitis the scotoma is central, while in papilledema the central field is
preserved until late; (3) there may be cloudiness of the posterior part of the
vitreous in papillitis; (4) swelling of the disk, venous engorgement and hemorrhages
are less pronounced in papillitis; (5) papillitis is usually unilateral and papilledema
bilateral, and (6) pain on pressure or movement of the eyeball is characteristic
of inflammation of the optic nerve.   CHODOFF, Langley Field, Va.

THE BRUNS SYNDROME. BERNARD J. ALPERS and H. E. YASKIN, J. Nerv. &
    Ment. Dis. **100**:115 (Aug.) 1944.

Alpers and Yaskin report 5 cases, in each of which the Bruns syndrome was
prominent and of great localizing value. In 2 of these cases there was a midline
medulloblastoma of the vermis, in 2 cases astrocytoma of the cerebellar hemisphere
and in 1 case disseminated sclerosis with probable involvement of the vermis by
a plaque.

The Bruns syndrome is characterized by the development of attacks of vertigo,
headache and vomiting on change of posture of the head, by freedom from
symptoms between attacks and often by constant anterior flexion of the head,
usually in the midline but at times with lateral flexion and rotation. Additional,
more variable, symptoms, such as amaurosis, teichopsia, tachycardia, respiratory
irregularity and syncope, may occur. The change in posture which produces the

symptoms may be brought about by a change of position of the head in relation to the body, by arising from a reclining to an upright posture, by turning from one side to another, by rotation of the head, by lying down or, indeed, by any change in position of the body in space. Passive movement of the head may be of diag-. nostic aid. In the vast majority of cases the Bruns syndrome indicates a lesion in the fourth ventricle or adjacent structures. The lesion is usually a tumor, but cysticercosus of the fourth ventricle or multiple sclerosis can cause the syndrome, and it has been reported with tumors of the third and lateral ventricles.

The pathogenesis of the symptoms is not clear, although it has been attributed to periodic blocking of the ventricular system on change of posture of the head. The authors suggest that irritation of the vestibular nuclei or pathways may be the mechanism responsible for the symptoms. CHODOFF, Langley Field, Va.

CEREBELLAR TYPE OF ATAXIA ASSOCIATED WITH CEREBRAL SIGNS. ALEX J. ARIEFF and LEO A. KAPLAN, J. Nerv. & Ment. Dis. **100**:135 (Aug.) 1944.

Arieff and Kaplan report 5 cases, in all of which there were displayed signs and symptoms of dysarthria, cerebellar ataxia, intention tremor, involvement of the pyramidal tract and, at times, dementia and convulsions. In 2 of the cases the condition was thought to be due to alcoholism; in 1 case the diagnosis of multiple sclerosis was considered, and the other 2 could not be adequately classified. A history of familial or hereditary tendency to the disease was absent in all the cases. CHODOFF, Langley Field, Va.

SLEEP PARALYSIS. PAUL CHODOFF, J. Nerv. & Ment. Dis. **100**:278 (Sept.) 1944.

Sleep paralysis is defined as consisting of brief periods of complete immobility and powerlessness occurring as a person is falling asleep or as he is awakening. The syndrome may be precipitated by terrifying dreams and may be accompanied with hypnagogic illusions. The characteristic features of the condition were seen in 2 patients, both of whom presented other manifestations of a narcoleptic nature. The similarity between sleep paralysis and cataplexy is probably more apparent than real. The author concludes that sleep paralysis is a nondiagnostic symptom which may occur in narcoleptic patients or independently in otherwise healthy persons and that it may be due to a variety of factors.

CHODOFF, Langley Field, Va.

Treatment, Neurosurgery

RECONSTRUCTIVE ORTHOPEDIC SURGERY FOR DISABILITIES ARISING FROM IRREPARABLE INJURIES TO THE RADIAL NERVE. LEROY C. ABBOT, J. Nerv. & Ment. Dis. **99**:466 (May) 1944.

Abbot describes the reconstructive operative procedures used by him in cases of irreparable damage to the radial nerve. The first of these is tendon transplantation to correct the wrist drop with inability to extend the fingers and thumb. The muscles utilized are the pronator teres, which is transferred from its insertion at the lateral border of the midshaft of the radius to the common radial extensors of the wrist, and the flexor carpi radialis and flexor carpi ulnaris, which are transplanted to the paralyzed extensor muscles of the fingers and thumb. The palmaris longus muscle may also be employed. The technic used is a modification of that devised by McMurray. After operation, the limb is held in a position of dorsal flexion of the wrist with fingers and thumb extended for a period of two weeks, during which time active contraction of the transplanted tendons is begun. The results of this operation are often very good. In certain cases the ability to dorsiflex the wrist remains weak and the hand grasp ineffective. In such cases arthrodesis of the wrist is employed as a supplementary procedure. This does not

interfere with rotation of the forearm and is attended with little incapacity, provided motion at the carpometacarpal joints has been preserved.

CHODOFF, Langley Field, Va.

INTRASPINAL THIAMINE CHLORIDE IN THE TREATMENT OF GASTRIC CRISIS OR LIGHTNING PAINS IN TABES DORSALIS. BENJAMIN H. KESERT and MAURICE O. GROSSMAN, J. Nerv. & Ment. Dis. **101**:372 (April) 1945.

Kesert and Grossman report the results of treatment of 8 patients with tabetic pains and gastric crises by means of intraspinal injections of thiamine hydrochloride. Injections were given up to three or four times a year in doses of 50 to 100 mg. After injection the pains were intensified for about twelve hours, but in all cases there was noticeable relief from pain for several weeks or months. No harmful effects of any kind were encountered.

CHODOFF, Langley Field, Va.

MALARIA IN NEUROSYPHILIS. J. ERNEST NICOLE, J. Ment. Sc. **89**:381 (July-Oct.) 1943.

Nicole reports on the treatment of 401 patients who were successfully inoculated with malaria by the intramuscular route for neurosyphilis. He found that malaria therapy alone gave a good recovery rate but that the addition of drugs gave even better results and that, while tryparsamide may be the drug of choice, other drugs help a great deal. Such combined drug and malarial treatment apparently fulfils the function that can be expected of it in at least 50 per cent of cases. Even patients with acute or advanced neurosyphilis can make a good recovery.

If the first attack of malaria does not produce a cure, a second or a third inoculation may be expected to do so. "Cure" in a serologic sense will be more frequent if the Wassermann rather than the more sensitive Kahn test is used. The Kahn reaction and the colloidal gold curve are the last to show improvement, whereas the protein content and the cell count are the first and the Wassermann reaction is in between.

MCCARTER, Boston.

Society Transactions

Pituitary Tumors and Their Treatment. DR. OSKAR HIRSCH.

From the standpoint of pathologic anatomy, tumors of the pituitary gland and its surroundings are: adenoma, craniopharyngioma, meningioma, chordoma, glioma, aneurysm, osteoma, chondroma, cholesteatoma and sarcoma, as well as syphilis, tuberculosis, actinomycosis, xanthomatosis, arachnoiditis cystica and hydrocephalus. The last-named processes are not tumors, but they act as such, deforming or destroying the sella. The anterior lobe only is the site of primary tumors, whereas the posterior lobe is the place of predilection of metastatic tumors.

Microscopically, adenomas of the pituitary gland, constituting about 90 per cent of all tumors, are benign. They do not infiltrate the neighboring organs except in a few cases, metastasis being extremely rare. Clinically, however, the adenomas have unlimited growth. They compress the chiasm and push the neighboring organs aside. They destroy the anterior lobe. Therefore the patients show loss of sexual function. Nearly all the chromophobic and 50 per cent of the eosinophilic adenomas are clinically malignant. Owing to the small size of the benign eosinophilic pituitary adenomas, the anterior lobe usually remains intact, and therefore the functions of the sexual organs are maintained.

From the surgical standpoint, all tumors of the pituitary region can be divided into four groups: 1. Suprasellar tumors, growths situated above the pituitary gland, which may remain normal. The sella is usually normal. The symptoms are choked disks and irregular visual fields. These tumors are approachable only by the frontal route. 2. Intrasellar tumors, growths limited to within the sphenoid cavity. The clinical symptoms are usually acromegaly, absence of visual disturbances and ballooning of the sella. These tumors are easily approachable by the endonasal route. 3. Craniosellar tumors, one part of the growth extending toward the brain and the other toward the sphenoid cavity. These tumors are approachable by both the frontal and the endonasal route. The clinical symptoms are bitemporal hemianopsia, atrophy of the optic disk and loss of sexual function. 4. Cystic tumors, growths which consist of, or contain, a cyst. Calcification is frequently visible in the roentgenogram. These tumors are easily approachable by the endonasal route.

I employ my endonasal method, with local anesthesia. By means of submucous resection of the septum, the anterior wall of the sphenoid cavity is removed, and the enlarged sella is exposed and opened. The tumor is removed by curettement and suction.

I have operated on 277 patients with this method in nineteen years. The mortality rate was 5.4 per cent, most of the deaths being due to meningitis, which nowadays can be prevented by use of the sulfonamide drugs and penicillin. Fifty-six patients (20 per cent) died of recurrences during the nineteen years; 194 (70 per cent) were alive at the end of the nineteenth year.

As it is impossible with any method, whether the transfrontal or the endonasal route, to remove a large tumor completely, I use radium to destroy the rest of the growth. Neurosurgeons use roentgen irradiation.

Exclusive roentgenologic treatment presupposes a solid tumor. This therapy is without any effect on cystic tumors, but 17 per cent of all tumors of the pituitary region are cystic. According to Dyke and Hare, roentgen therapy produced

improvement in 26 per cent of patients with chromophobic tumors (47 per cent became worse) and in 40 per cent of the patients with eosinophilic tumors (24 per cent became worse). There are some instances of occurrence of cataract two to seven years after irradiation.

Advantages and Disadvantages of the Transfrontal and the Endonasal (Transphenoidal) Method.—The statistics for the Cushing series, as reported by Henderson, and for my series are tabulated here.

Series	Mortality
Cushing: 227 transphenoidal operations	5.3
101 transfrontal operations	4.5
Hirsch: 277 endonasal operations	5.4

The transfrontal method is the procedure of choice for all suprasellar tumors without widening of the sella. To all other tumors the endonasal method is applicable.

The treatment of cystic tumors is much easier with the endonasal method, and the reopening of the cyst by this route is also an easy procedure.

With either method, with the endonasal (transphenoidal) or with the transfrontal, an intracranial tumor cannot be removed entirely. To prevent the further growth of the remaining tumor tissue, the neurosurgeon uses postoperative roentgen therapy. I apply radium locally. My results have been as follows: 1. Of patients who had the endonasal operation plus radium irradiation, 76 per cent remained free from recurrences over four years. 2. Of patients who had the transfrontal operation plus roentgen irradiation, 87 per cent remained free from recurrence until the end of the fifth year.

Henderson's figures, based on Cushing's material, show 57 per cent of patients alive two to twenty years after operation; my figures show 70 per cent.

With the transfrontal method, postoperative clotting in the operative field, especially with cystic tumors, appears in 14 per cent of cases. This clotting produces pressure on the optic nerves and, according to Henderson, is the most serious objection to this method.

The transfrontal method gives poor results in cases of homonymous hemianopsia and central scotoma, which constitute, respectively, 7 and 11 per cent of cases of pituitary adenoma.

With the transfrontal method one meets difficulties in the case of a prefixed chiasm. In these circumstances the exposure of the tumor requires transection of the chiasm. Prefixed chiasm is present in 5 per cent of cases of tumor in this region.

With the transfrontal method one risks the development of transient or permanent mental symptoms in elderly people with shrunken convolutions and a dura strongly adherent to the bone (Cairns).

The endonasal method is performed without any external scar and can be done with local anesthesia.

The objection to the endonasal method is a spongy sphenoid bone (rare with pituitary tumors).

Both the transfrontal and the endonasal method carry a postoperative risk, namely, clotting with the transfrontal method and meningitis with the endonasal method. Since meningitis can be checked by chemotherapy, the endonasal method should be considered in all cases of pituitary tumor in which surgical treatment is indicated.

DISCUSSION

Dr. Gilbert Horrax: I should like to pay my respects to Dr. Hirsch. It is recognized that he is one of the pioneers in the attack on pituitary tumors, and his endonasal method, or modifications of it, are used by many neurosurgeons in operating on adenomas of the pituitary gland. I must apologize for not having statistics on the subject, but I should like to discuss this paper from several aspects.

First, as neurosurgeons we see essentially three types of pituitary tumors: chromophobic adenoma; eosinophilic adenoma, which produces acromegaly, and the

rare basophilic adenoma. I have operated on only 1 adenoma of the last type. Patients with chromophobic adenoma usually come to the surgeon or the neurologist because of trouble with vision. If the patient is a woman, she may have had amenorrhea for a long time, and some patients have other glandular symptoms. The acromegalic patients are concerned chiefly with the changes in their features. I am leaving out of consideration all other types of tumors in the pituitary region, as time does not serve to discuss them.

It is difficult to decide whether one should operate or try roentgen therapy. The transfrontal or the endonasal operation served a great purpose in the early days of attack on these tumors. Whether operation is still of value in certain cases I am not sure. Very likely there are selected cases in which it should be used. Having seen Cushing use the transsphenoidal approach and later abandon it for the intracranial operation, and in view of the better exposure which is possible with the latter, I feel one can almost always accomplish more with this method. There are certain cases in which a prefixed chiasm gives little room, but in my experience one gets a much better exposure by working from above. A rhino-laryngologist like Dr. Hirsch, working perhaps with a special light and other adjuncts, can do a great deal in some cases.

The important thing in Dr. Hirsch's statistics is the number of recurrences and the number of patients who died of recurrence in the first few years after operation. As far as the immediate mortality rate is concerned, there is little to choose between the transfrontal and the transphenoidal operation, but the problem lies in obtaining a radical extirpation of the tumor. It seems to me that a much better cleaning out of the tumor is possible by the intracranial route. In a case of cystic tumor, the cyst will refill if any remnant of the wall is left behind. It is important to remove all of the wall. One must strive for as complete an evacuation of the tumor as possible and take out the capsule above the sella. Leaving aside all technicalities of the approach, there may be a few selected cases in which the tumor has grown downward and one can get at it better through the nose. But most neurosurgeons now are not very familiar with the endonasal route. It is rare that one has to operate for acromegaly. It is indicated only in the incipient stage, in younger patients with early facial changes. I think acromegalic patients do better with roentgen irradiation. It also helps their headache.

It is difficult to decide when one should operate on an adenoma. One has to be guided by the individual case. There is a mortality for any operation. In cases of the ordinary chromophobic type the mortality should be less than 5 per cent. In cases of "malignant" extensive adenoma there is a high mortality rate, but therapy is not of much value anyway. For the patients who have moderate visual disturbance and can still earn their living I suggest roentgen irradiation first. I always give them the benefit of a trial of roentgen therapy under careful supervision. It is my impression that probably about 25 per cent of such patients get sufficient help from roentgen therapy; hence, a trial of this method is warranted. Some patients get great visual relief from it, and some get relief from headache. When patients who are receiving roentgen irradiation continue to have visual acuity of 20/40 to 20/50 or less, the result cannot be considered good, and such a patient almost certainly should be operated on. On the other hand, one has to remember that even though roentgen therapy may carry a patient along fairly well for many years, the tumor may nevertheless be spreading and the time will come when neither irradiation nor operation will help. All in all, I do not feel very happy about the results of roentgen treatment of pituitary tumor except in patients who respond promptly and well. The surgeon has to decide in the individual case, but the problem is an interesting one and more is being learned about it. My own feeling is that I know much more about the intracranial than the transphenoidal route, and I should prefer to attack all pituitary tumors in this way. The figures Dr. Hirsch gave for Dr. Cushing's series were for his early work. It is extremely rare to have a postoperative clot now.

Dr. James L. Poppen: I enjoyed the paper very much. It is rather preposterous of me to say anything on this subject. Whereas Dr. Hirsch has an

experience of thirty years, with twenty years of postoperative observations, I have only twelve years. I have nothing to add to Dr. Horrax' discussion except to elaborate on the dangers of roentgen irradiation. I feel that this treatment is of value in very early stages. I had a patient in the last six weeks who began roentgen treatment two years ago. His vision was on the borderline at that time. He did not want to be operated on then. Therefore I temporized with him and gave him roentgen radiation. After the first treatment his vision improved slightly, and his headaches improved. He was pleased with the result. Six months later his vision became poorer and his headaches were worse. A week later scintillating scotomas developed. This symptom persisted four or five days and then disappeared, and his headaches improved. Six weeks ago he had another series of treatments, again resulting in scintillating scotomas and blindness. An emergency operation was performed, and a large hemorrhage into the adenoma was evacuated.

More recently I have had a patient who received roentgen treatment; his condition grew worse, and he died before operation could take place. One must keep in mind that roentgen therapy has also a definite mortality rate. The visual fields should be watched carefully during treatment.

CAPT. JAMES C. WHITE (MC), U.S.N.R.: A case which my associates and I had recently in the Naval hospital illustrates one of the complications for which one could not do much by the intranasal approach to the pituitary. The man had had bitemporal hemianopsia with increasing visual disturbance since 1938, together with evidence of hypopituitarism. Distinct personality changes had recently developed, and a series of generalized epileptic fits followed. The cause of these symptoms was an adenoma of the pituitary gland, which had grown out of the sella turcica and extended forward to the crista galli and caudally to the middle portion of the pons. It weighed 150 Gm. Jefferson, who has given the clearest account of such unusual parasellar extensions of pituitary adenomas (*Proc. Royal Soc. Med.* **33**:433-458, 1940), reported that they occur in approximately 14 per cent of cases of pituitary tumors, particularly of the chromophobic type. Since the tumor may grow upward into the hypothalamus, forward between the frontal lobes, backward beneath the tentorium and, most commonly, laterally into the temporal lobe or the cavernous sinus, such extension may often be missed clinically and can then only be found at the time of the operation if the approach is made by the frontal intracranial exposure. In such circumstances little, if anything, could be accomplished by the endonasal route.

DR. OSKAR HIRSCH: Most neurosurgeons will not use the endonasal operation because they are not familiar with this method, as I am not familiar with the neurosurgeon's method. The point I wish to make clear is that, according to the figures on recurrence and mortality which I presented, the two methods are equally successful. There is no reason to neglect a method which has been employed in the greatest number of pituitary tumors. If operation is indicated in a case of pituitary tumor, both methods must be considered.

Neurocirculatory Asthenia, Effort Syndrome and Anxiety Neurosis. DR. STANLEY COBB, DR. PAUL D. WHITE, DR. MANDEL E. COHEN, DR. DANIEL W. BADAL, DR. WILLIAM P. CHAPMAN and DR. ROBERT E. JOHNSON.

The clinical picture of neurocirculatory asthenia consists of a large number of symptoms, which occur frequently. These include not only cardiovascular-respiratory disturbances but symptoms commonly seen with neuropsychiatric disease. Failure to recognize the broad nature of the symptoms has led to much confusion in the literature.

The disorder consists of two types, the chronic and the acute. Our studies have dealt primarily with the chronic type, represented by patients who were unable to do hard work and who had been emotionally unstable as long as they could remember. The chronic type of neurocirculatory asthenia shows a strong familial tendency. Studies of normal control soldiers and sick soldiers with osteomyelitis do not reveal this tendency.

Work tests (treadmill and step) have been used to determine the amount of hard work that can be expected from the patients. Patients do poorly on these tests as compared with normal control subjects. The lactic acid response after moderate exercise (treadmill walk) gives a mean of 43.6 mg. per hundred cubic centimeters for the patients and a mean of 21.6 mg. per hundred cubic centimeters for the normal controls. Studies of respiration and response to exercise show that the minute respiratory volume is greater in the patients than in normal control subjects, as illustrated by the Harrison ventilation index, which demonstrates that there is an objective correlate of the patient's subjective feeling of dyspnea. The response of the pulse to exercise shows a higher rate and a slower return to normal. Studies of the capillaries of the finger nail bed show that the patients have fewer hairpin forms and more looped and unusual forms than do the normal control subjects. The incidence of hairpin forms in normal, healthy soldiers is 79 per cent; in soldiers convalescing from wounds complicated by osteomyelitis, 65 per cent, and in patients with neurocirculatory asthenia, 42 per cent.

Studies of reactivity to pain, ability to maintain a sustained grip and willingness to stand unpleasant electric shock all yield low values for patients with this disorder. This suggests that the patient's disability is not limited to the cardiovascular apparatus alone.

Psychologic tests give scores placing the patients in the group labeled "neurotic."

The evidence suggests that the chronic type of neurocirculatory asthenia is a disorder which runs in families; symptoms extend over years of the patient's life, and exacerbations may be provoked by hard work, acute emotion-provoking experiences, chronically emotion-disturbing situations, infection and perhaps other factors.

DISCUSSION

Lieut. Comdr. Herbert I. Harris (MC), U.S.N.R.: It is a privilege to be invited to discuss this paper by Dr. Cobb and his associates, and I am much impressed with the varied points of departure from which this problem has been approached. This approach is in the best tradition of the holistic, or psychosomatic, discipline.

The tyranny of words interests me deeply, and the criticism of the word "psychosomatic," which Dr. Cobb expressed, makes me wonder whether he may not have overlooked a value of this word which is not shared by the word "holistic." The word "holistic," it is true, is of earlier origin and in some respects is more inclusive than the word "psychosomatic." All must agree, however, that the familiarity of the elements in the word "psychosomatic" have made it much more acceptable to members of the medical profession at large and has resulted in a striking increase in the interest paid by the nonpsychiatric members of the profession in the emotional disturbances which accompany all forms of disease. It is on the basis of this pragmatic usefulness of the word "psychosomatic" that I should like to register a plea in its favor.

I feel that at this point I should rise to the defense of the Navy, since views opposing those expressed in Master's paper, referred to by Dr. Cobb, appear in an article by R. R. Steen, published in the February 1944 issue of the *United States Naval Medical Bulletin,* page 353, in which the author speaks of the effort syndrome as being nothing more than an anxiety state. Certain it is that the effort syndrome has an intimate relationship to war. If I recall correctly, primitive man used to consider it a good idea to eat the heart of his enemy in order to have his enemy's courage. It is evident that these sufferers from the effort syndrome are not planning to have their hearts eaten if they can help it. Another striking factor in this syndrome alines itself with my own attitude toward these conditions. It may be noticed that all the symptoms Dr. Cobb has enumerated are suggestive of an egocentric attitude on the part of the sufferer. They represent, in other words, a turning of the patient's attention toward himself. This response is typical of the neurotic patient, and I believe all are in agreement that the emotional factors in this condition are of the utmost importance in its genesis.

The neurophysiologic aspects of the effort syndrome cannot be neglected, and it is heartening to note the emphasis placed on them in Dr. Cobb's paper. It is always a good idea to keep in mind that cortical influences on the hypothalamus might well be able to produce all the signs and symptoms of this disorder.

My colleagues and I have noticed in our studies on a group of persons suffering from neurocirculatory asthenia that the men in their forties who had had no previous history of heart consciousness but who had been exposed to intense tropical heat exhibited the effort syndrome after some time. Coincident with its onset they noticed a loss of libido. I wonder, therefore, whether a deficiency of circulating androgens may be a factor in this disorder. Dr. Cobb mentioned that most of the normal control subjects tried to date the laboratory workers, whereas the group of men with the effort syndrome showed relatively little interest in these girls. It seems reasonable to assume the presence of a greater amount of libido in the controls than in the patients. I wonder whether Dr. Cobb has considered making an androgen-estrogen assay on these patients. It is possible that the metabolism of lactic acid is somehow related to the androgen composition of the blood, since athletes in training acquire increased muscle mass and poorly developed adolescents with hypogonadism frequently show a striking increase in muscle mass after androgen therapy.

Dr. Felix Deutsch: I should like to ask a question which is chiefly related to the physiologic side. I made observations on many hundreds of normal patients. Many had a family history of symptoms not only of neurocirculatory asthenia but of heart disease. I found that the basal metabolic rate returned to normal much more slowly in such persons than in normal persons. The patients who had small arteries did not show a decrease in size of the heart. The heart becomes smaller after effort, but the patients showed dilatation of the heart much sooner, and this increase of size persisted longer than in normal persons.

Excessive self observation of the heart is a kind of hypochondriasis. These patients show a tremendous amount of anxiety, like people who are continually running away from danger, and it is expressed by this kind of reaction of the vasomotor system.

Dr. Paul I. Yakovlev, Waltham, Mass.: I note that, while the symptoms of neurocirculatory asthenia are motivated by emotional factors, they seem to be precipitated mostly on the occasion of locomotion rather than by other patterns of motor activity.

Dr. Stanley Cobb: I ought to emphasize that these men can show the syndrome as much on emotional stimulation as on locomotion. Locomotion is no more likely than lifting to produce the symptoms.

Dr. Robert E. Johnson: To answer Dr. Deutsch's question: Oxygen deficiency was not measured in these men, and I do not think that the size of the heart was measured before and after exercise.

I should like to emphasize a point which Dr. Cobb omitted. It is the question whether these patients can be trained physically. It was apparent that they were in poor physical condition, with poor stamina for ordinary work and for standard tests. Everything we measured in them gave values inferior to those for the controls. The question whether they would not or could not work was answered to our minds by the fact that even in work which they could endure for the same length of time as normal controls, their performance was worse in every respect. An attempt was made to train them in order to see whether they were capable of improvement or fell into the physiologically inferior group. In any freshman class at Harvard about 10 per cent are in poor physical condition. Of this 10 per cent, a large number can be trained into reasonably good condition, but the state of some remains poor no matter how much they train physically. Two groups of 15 patients with neurocirculatory asthenia were subjected under Mr. Cox to the same type of training as is given the Harvard freshman. Neither cajoling nor threats of Army discipline would induce them to work hard enough to improve. Although the experiment was inconclusive, our feeling is that these patients are incapable

of any but slight improvement on training and are intrinsically inferior from the physiologic standpoint.

DR. DANIEL BADAL: With regard to heart disease in the family, there were about 7 per cent with angina pectoris both in the group with neurocirculatory asthenia and in the normal group. In some cases we examined the parents of patients. Some of these persons had had neurocirculatory asthenia for thirty years, but none had bad hearts. Among parents of the control group we found 1 parent with rheumatic heart disease.

DR. STANLEY COBB: Dr. Harris spoke of the importance of the emotional state. We think that it is extremely important. These men were introverts; they had their minds on themselves. They were hypochondriac; they had their minds on their hearts because a large number had had the experience in youth of having symptoms referable to the heart and of being warned to be careful of it. The overlap of the emotional and the locomotive aspect is exemplified by the case of 1 man in particular. I liked him, and it was easy to sit and talk to him. In youth he had had trouble after exercise. After he was in the Army he had it, but it was much more on the emotional level. He was most afraid of inspection. In the laboratory we hooked him up to machines for recording respiration, skin resistance and heart rate. I had him lie there for five minutes and think about anything he wanted to. Then I told him to think about fishing in a river in New Hampshire, and his respiration and heart rate quieted down and his skin resistance fell. Then I told him, "You are on inspection, and the officer is coming down the line. He is looking at this man and at that man, and pretty soon he will get to you." The respiratory record became irregular and rapid, with big sighs. The heart speeded up, and the skin resistance dropped sharply. His attack had come on like a conditioned reflex. In some subjects it was obvious that they had the attacks because of effort, but they could also have them when they were sitting in a chair or lying in bed.

As to androgens, we are working on that now, testing the 17-keto steroids.

DR. DANIEL BADAL: Some patients had been exposed to extreme heat in the tropics and some to extreme cold, as in the Aleutians. They mentioned that extremes of heat and cold would bring on the symptoms. The two were equally bad.

DR. STANLEY COBB: Of course we had to rule out any men who were convalescent from some recent illness, especially malaria.

PAUL I. YAKOVLEV, M.D., *Presiding*

Regular Meeting, Jan. 18, 1945

Essential Male Homosexuality and Results of Treatment. DR. ABRAHAM MYERSON and DR. RUDOLPH NEUSTADT.

By the term "essential male homosexuality" it is implied that this condition is constitutional and is manifest consciously and early in the development of the patient, usually before or at puberty. In cases of this condition the male arouses sexual passion and desire, and if there is any capacity for sexual relationship with, and even love for, the female, it is feeble as compared with the desire for the male and is undertaken only to be normal or for social purposes. The term "conscious homosexuality" means that there is excluded from the discussion such "homosexuality" as is disclosed by analysis and rests on inference and symbolism.

In our previous publication (Androgen Excretion in Urine in Various Neuropsychiatric Conditions, ARCH. NEUROL. & PSYCHIAT. **44**:689 [Sept.] 1940), and in Needham's book, the relationship of the male and female hormones, which are present in both sexes, to cholesterol and to each other is shown, and it is obvious from a study of the chemical structure of these hormones that their similarity bespeaks a common origin. In previous papers we stated that essential male homosexuality is associated quite constantly with a low excretion of male hormones

and a relatively high excretion of female hormones. At that time we pointed out the essential difficulties of reaching this conclusion. Time and experience have shown that the conclusion went too far. There are many reasons for the failure of experience to corroborate completely our expressed point of view. The first is the nonspecificity of the chemical tests for the male and female hormones in the urine, since there are many substances not active hormones which are not differentiated by these tests. Furthermore, there are men who are not homosexual who present similar hormonal values. In our experience these persons are not normal and in general represent impotent males. That the tests have some clinical value, despite their failure to be specific and final in the determination, is shown by the fact that most of the male homosexuals we have studied have shown a lack of androgens and usually an excess of estrogens, both these terms being used to include the nonactive substances which are present.

In previous publications we stated that treatment with hormones had been disappointing. Wright and, later, Lurje reported success with the use of male hormones in changing the reactions of the homosexual male. In the past year one of us has treated 15 persons with essential male homosexuality with a relatively new preparation of the male hormone, a 10 mg. tablet of methyl testosterone, to be dissolved in the mouth. The present standard dose for these patients is 20 mg., or 2 tablets per day, taken each day for two months, with a resting period of two months. This resting period is recommended on the basis of work done by Zondek, in which he showed that antihormonal properties are evoked by the continued use of hormones.

The results have been interesting and at the same time puzzling. With 2 of these subjects no effect was obtained. These 2 men stated that they felt no difference, that their homosexual drive was as consistent and as compulsive as before. With the other 13 patients distinct results were obtained, according to the statements of the patients. In all of them the homosexual feeling disappeared or became greatly lessened. As one man stated, "It was almost as if an antidote had been administered." In only 5 of these patients, however, was a direct heterosexual drive established, and in none of them was it sufficient to bring about a successful heterosexual life. In 1 of these patients this result was extremely welcome, since the man was a priest to whom this neutral state was restful. In a young boy with pronounced gynecomastia and a severe obsessive-compulsive state, in addition to the driving homosexuality, the drive has entirely disappeared, and he is no longer disturbed by homosexual feelings, although he has, practically speaking, no vivid heterosexual feelings and his obsessive-compulsive state has shown but little change. In a homosexual man who became greatly depressed, independently, I think, of his homosexuality, the homosexual feeling disappeared during the depressed stage, just as heterosexual feeling disappears in sexually normal depressive persons. As he started to recover, homosexual feelings returned, but they are controllable with the methyl testosterone. In a man whose anxiety state seemed related to his complicated social status because of his homosexuality, the administration of the testosterone, by eliminating the homosexual feelings, appeared to do away with the anxiety as well, although this is entirely inference.

In all the cases it has been necessary to administer the preparation every two months. The treatment is too recent for any definite statement to be made about the future of these patients. It does not seem likely, on the basis of past experience with the parenteral administration of hormone and the knowledge gained in this series of cases, that in the adult male homosexuality can be completely cured by use of present day preparations of hormones, although they more easily modify it than does any other form of treatment. The failure to cure impotence in males by use of hormones indicates that some other mechanism is involved in the disturbance of direct heterosexual desire in the case of the deviate or sick male.

DISCUSSION

Dr. Rudolph Neustadt: Dr. Myerson has pointed out the difficulties with which the biochemical approach to a personality problem, such as homosexuality, is

beset. I do not want to repeat his statements, but I should like to stress the close relationship of the various substances with "androgenic" and "estrogenic" activity. One is in a precarious situation in that one is not able to differentiate how much of each of these substances is present in a specimen of urine. One simply measures the total amount of these substances. This, of course, is a great disadvantage; however, I do not expect a real progress in this field for some years. On the whole, the biochemical approach to endocrinologic problems, outside of gynecology, has lagged far behind the experimental work. In the attempt to approach a psychiatric problem from the biochemical side the difficulties are multiplied. One does not know how much the personality affects the formation and excretion of hormones; one knows practically nothing of what different kinds of food, different exercise, swings of mood, sexual abstinence or sexual activity do to the hormone level. It is difficult to observe these factors under experimental conditions. It is just a matter of impressions, gained by chance observations.

The treatment of homosexuality with endocrine preparations suffers from a disadvantage common to all endocrine therapy; i. e., the commercial products are not identical with the actual substances present in the organism, nor do they act in an identical manner. It is probably a different biologic action, through which Dr. Myerson was able to improve his therapeutic results by using methyl testosterone instead of the older testosterone propionate. Further modifications may give still better results.

Intracranial Aneurysm in Fifty-One Proved Cases. Dr. James L. Poppen.

Intracranial aneurysm is one of the most deadly conditions affecting the intracranial cavity and has been treated by most neurosurgeons in the past by watchful waiting. In recent years Dandy has stimulated consideration of actual surgical intervention by either direct or indirect attack on the aneurysm and has demonstated that it is a condition which can in many instances be cured by surgical means. Symonds (*Guy's Hosp. Rep.* **73**:139 [April] 1923) should receive considerable credit for emphasizing the history and physical manifestations produced by intracranial aneurysm.

The etiologic factor in intracranial aneurysm is predominantly congenital. Several excellent reasons for their development have appeared in the literature. Fetterman and Moran found that the circle of Willis was like that described in the anatomic textbooks in less than 50 per cent of cases. Many variations and anomalies were observed, involving mainly the posterior communicating artery. Glynn noted that the elastic tissue was predominantly concentrated in the internal elastic lamina rather than being uniformly distributed throughout the media and adventitia, as in other arteries of the body. Bremmer suggested that stimulation of the growth of the walls of the blood vessel by mechanical pulsations inside the artery and the resulting change in angulations of arteries, which in the embryo are acute and later become almost right angles during the developmental stage, are factors in producing congenital weakness at the bifurcation. He stated the belief, also, that the transitional remnants of vessels, having little pulsation, are therefore particularly vulnerable to development of aneurysm. This opinion is also entertained by Dandy.

Syphilis played no part in the formation of aneurysm in the 51 proved cases. That syphilis was a relatively unimportant cause was indicated as well by Dandy's series and by the 1,023 collected cases of McDonald and Korb. In 10 of our cases the aneurysms occurred in patients with hypertension and associated arteriosclerosis. That trauma plays no part, or only to a slight degree, in causing either the aneurysm or the rupture of aneurysms is emphasized by the study of Magee in 150 cases. The condition predominates in the female (34 females; 17 males in the present series). The right side was involved in 18 cases and the left in 33 cases. The diagnosis is made from the history and clinical signs. The classic picture is that of periodic bouts of unilateral headache or unilateral neuralgic pain in the face, eye and forehead. The actual rupture is manifested

by the classic signs of subarachnoid hemorrhage. The larger aneurysms involving the internal carotid artery may show signs of tumor in the region of the sella turcica. Roentgenograms of the skull show changes only when the aneurysm has reached such a size that it erodes bone in the region of the sella turcica and is manifested by unilateral destruction of the clinoid process and upward displacement of one of the anterior clinoid processes. In a few cases crescentic calcification makes the diagnosis of aneurysm almost certain. However, other tumors may have similar calcification and be mistaken for aneurysm. Seventy-five per cent of intracranial aneurysms involve the anterior two thirds of the circle of Willis. The internal carotid artery and the middle cerebral artery seem to be the most vulnerable, although the anterior cerebral artery is also commonly involved.

It is unfortunate that the symptoms of an intracranial aneurysm in many instances are initiated by a spontaneous subarachnoid hemorrhage. Magee found that 52 of 150 patients with subarachnoid hemorrhage died during the primary attack. Fifty of the 98 survivors of the first attack had a recurrence, and 32 more failed to recover, indicating the seriousness of the entire situation.

It is evident that actual surgical attack can be intelligently applied only in patients with typical histories and clinical signs. However, in the surgical attack, it is of value to know the exact location of the aneurysm, as well as its origin. Decision can then be justly made as to whether the aneurysm can be trapped between ligatures with reasonable safety or whether it must be attacked indirectly by ligation of the large vessel in the neck to avoid making the patient a hopeless cripple after operation. In many patients there are no focal signs. It is logical, therefore, to visualize the arterial tree intracranially; and since no untoward results have been noted, either at the time of injection or later, with thorotrast, we feel that it is indicated for accurate location of the aneurysm, and thus as an aid in the decision as to treatment. Also, its use has assisted in making the diagnosis definite.

Before surgical intervention, it is important to determine whether the collateral circulation on the side on which the aneurysm is located is adequate and whether there are any anomalies. This can be done by compression of the carotid artery, the pressure being applied over the great vessels in the neck and graduated so that the patient is able to tolerate complete compression for ten minutes three times a day. The compression also helps in determining whether the patient has an irritable carotid sinus which may cause untoward signs, which may be erroneously interpreted as indicating that the patient is unable to tolerate compression.

Direct attack and excision of the aneurysm itself are, of course, the procedure of choice if indications are that it will not leave the patient a permanent cripple. The indirect attack by ligation of the common or internal carotid artery is then the only alternative. Partial ligation of the arterial flow through the internal carotid artery can be accomplished by ligation of the common carotid artery, which cuts down only 50 per cent of the blood supply to the internal carotid artery. If more complete occlusion can be tolerated, the internal carotid artery itself can be ligated. If the internal carotid artery cannot be safely ligated, the common carotid artery, as well as the external carotid artery, can be ligated, leaving the superior thyroid and lingual arteries intact, so that they allow collateral circulation into the internal carotid artery.

After ligation it is important to keep the patient in the Trendelenburg position in an oxygen tent, so that the blood which does enter the cerebral hemisphere is well oxygenated. The patient must be carefully watched. If late unilateral symptoms appear, heparin is given immediately to prevent ascending thrombosis or embolism.

Slides were shown to demonstrate the various characteristics of aneurysms involving the internal carotid, the middle cerebral and the posterior communicating arteries. Slides were also shown of two aneurysms that had been completely extirpated.

DISCUSSION

Dr. Charles Kubik: I have been much interested in Dr. Poppen's paper and the lantern slides of his unusually clear arteriograms. Several years ago Dr. Ayer and I went over the records of a group of cases of spontaneous subarachnoid hemorrhages—most of which, one may assume, were due to leaking or ruptured intracranial aneurysm—and found the mortality not nearly so high as that given by Dr. Poppen. I think that it was 28 per cent for all patients with spontaneous subarachnoid hemorrhages admitted to the hospital. I know of no follow-up report on a large series of cases over a long period, though all know patients who have recovered, without operation, and remained asymptomatic for ten years or longer. It seems to me that the results of both medical and surgical treatment in larger groups of cases for longer periods will have to be analyzed before a comparison of the two methods of treatment can be made. There is, of course, no doubt of the benefit derived from operation when it provides relief of pain. Dr. Poppen's results, with respect to complications which may follow ligation, have been surprisingly good.

Dr. D. Denny-Brown: I am glad Dr. Poppen has emphasized the seriousness of intracranial aneurysm. Perhaps arterial ligature is not advised as often as it might be. It appears to me that the most serious subarachnoid hemorrhage arises frequently from aneurysm of the anterior communicating artery when the side of the lesion is in doubt, or from the junction of the posterior communicating and the posterior cerebral artery. Further, it is my impression that the most dangerous aneurysms are quite small. The period of difficulty in decision is soon after a leak. Has Dr. Poppen found any evidence that thorotrast damages vascular endothelium, and would he advise its use to localize the aneurysm in such an early stage? What would Dr. Poppen consider to be a contraindication to arteriographic examination?

Dr. Paul B. Jossmann: I should like to ask Dr. Poppen whether he has had experience with the further development of aneurysms after ligation, particularly with respect to their pathologic changes. I wonder whether, by establishment of collateral circulation, retrograde refilling of the aneurysm takes place after a certain period.

Dr. Abraham Myerson: I should like to ask Dr. Poppen to give us more details of his injection of thorotrast. When I was using the method, I did not get such beautiful pictures.

Capt. James C. White (MC), U.S.N.R.: As far as arteriovenous aneurysms are concerned, the results which my associates and I have had with ligation of the common carotid artery have been discouraging. Of 6 cases of this type, bruit recurred in 3 and hemiplegia developed in 1. From this experience I do not see how ligation of even the common carotid artery can be considered a really safe procedure. The case of complicating hemiplegia was in a woman of 40, who tolerated thirty-six hours of preliminary occlusion with a band of fascia around the common carotid artery. The second day we reopened the incision and cut the previously occluded artery between two ligatures. Hemiplegia developed during the night, twelve hours after the second, and final, ligation.

Dr. H. Hale Powers, Wellesley, Mass.: I should like to ask about the age when the initial hemorrhage occurred in the patients. Has Dr. Poppen any data as to what effect on mental capacity ligation has had?

Dr. William Jason Mixter: Captain White knows more about this than I do. I think it is a beautiful piece of work, and I am particularly interested in the excellence of the roentgenograms which he has obtained. He leads the way, and even if our statistics have not been as good as his, we should follow his lead and endeavor to improve our results.

Dr. James L. Poppen: My associates and I have used thorotrast in small amounts, using 10 cc. for the stereoscopic film. We have seen no early or late

effects from its use. The ability to obtain stereoscopic pictures of the aneurysm can be accomplished only by enthusiastic and intelligent assistance of the x-ray department. We are fortunate in having the cooperation of Dr. G. A. Marks, of the New England Deaconess Hospital, and his group of technicians have helped me tremendously. Dr. H. F. Hare and his technicians at the New England Baptist Hospital have been equally helpful. There is no reason that excellent films cannot be obtained if there is intelligent cooperation between the x-ray technicians and the surgical team. I see no contraindication to ligation of the large vessel in the neck in a patient who has a large aneurysm as long as one knows that he is able to tolerate occlusion of the vessel, and this can be done by watching the patient under local anesthesia at the time of the contemplated ligation. If the patient is able to tolerate occlusion for at least one-half hour, one can assume that it is safe to ligate. This rule, of course, is not absolute. One must continue to watch the patient even after he has been returned to the ward to be sure that no hemiplegia takes place.

In answer to Dr. Jossmann, it is my impression that whenever the direct pulsations on the aneurysm can be diminished, there is less danger of rupture.

In regard to Captain White's patients in whom hemiplegia developed after ligation of the common carotid artery, I feel that this tragedy can be avoided by the use of dicoumarin (3,3-methylene-bis-4-hydroxycoumarin) and heparin. Use of the dicoumarin may be started on the second postoperative day. It certainly should prevent ascending thrombosis. Whether it actually would avert an embolus I am uncertain, but I believe the chances of the development would be definitely less. Certainly, if hemiplegia develops after ligation of the common carotid artery, it will also develop after ligation of the internal carotid artery, so that I cannot see why the common carotid artery may not be attacked surgically, since it reduces the blood supply to the brain only 50 per cent in most cases.

The initial hemorrhage occurred at no particular age in our patients. The youngest patient was 15 years of age and the oldest 69. There has been no effect on the mental capacity following ligation to date. We have had no operative deaths; however, complete hemiplegia resulted from ligation of the internal carotid artery in 1 case.

News and Comment

ALFRED ULLMAN LABORATORY FOR NEURO-PSYCHIATRIC RESEARCH

The Sinai Hospital, of Baltimore, announces the establishment of the Alfred Ullman Laboratory for Neuro-Psychiatric Research. The work in the laboratory will be carried out under the direction of Dr. H. S. Rubinstein.

AMERICAN SOCIETY FOR RESEARCH IN PSYCHOSOMATIC PROBLEMS

The annual meeting of the American Society for Research in Psychosomatic Problems will be held at the Hotel Pennsylvania, New York, May 11 and 12, 1946. "Contributions of Military Medicine to Psychosomatic Medicine" will be discussed in the morning and "Psychosomatic Aspects of Orthopedic Practice" in the afternoon of the first day. After the annual dinner an illustrated parody on "New Advances in Psychosomatic Investigative Technics," by Dr. Bertram D. Lewin, will be presented. On May 12 there will be volunteered contributions.

Because of space limitation, reservations should be made at least two weeks prior to the meeting. Further information may be procured from Dr. Roy G. Hoskins, chairman, program committee, 714 Madison Avenue, New York 21.

Book Reviews

Experimental Catatonia. A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology. By Herman Holland de Jong, M.D., with forewords by Nolan D. C. Lewis, M.D., and David T. Smith, M.D. Price, $4. Pp. xlv, plus 225, with 15 tables and 38 figures. Baltimore: Williams & Wilkins Company, 1945.

Since the discovery by the author in the 1920's that bulbocapnine was capable of reproducing the motor phenomena seen in catatonia, de Jong has pursued his researches with a number of collaborators and in various localities. The present work is an extension of the investigations published with Baruk (*Rev. neurol.* **2:**532, 1929). De Jong has found that, far from being a specific effect of bulbocapnine, catatonia is a general reaction form attributable to disturbances of function of the central nervous system and that it may be produced by a wide variety of chemical and physical methods. Many drugs have been tested under varying circumstances, and the author has shown that in many instances, in the twilight· zone between life and death produced by the administration of slightly sublethal doses, the animal responds with catatonia. It may be significant that a still higher dose provokes convulsive seizures, sometimes eventuating in death. Anoxia almost certainly plays a part in the genesis of the symptoms, because they may be elicited by experiments leading to anemia, anoxemia and other deleterious influences on the central nervous system. Centrifugation, electronarcosis and cerebral resection may also induce catatonia. Chilling and heating would seem to be worth investigating.

One misses in this volume a consideration of the effects, particularly the psychologic ones, that are induced in man by the administration of bulbocapnine to normal and "precatatonic" persons. A tantalizing glimpse is given of the exaggerated effect of bulbocapnine in animals who have undergone small or large cortical extirpations.

De Jong reports on a number of blind alleys. For instance, the urine of certain schizophrenic patients contains a substance that is capable of producing catatonia in mice. After laborious research this substance was finally identified as nicotine and was found to be present in considerable amounts in smokers, but not in those who were not exposed to tobacco. The role of histamine held promise for a time, but further researches ruled out this substance as an important contributing factor.

The author is somewhat overly generous in detailing technical methods and protocols. These seem to belong, rather, in briefer papers, where investigators who wish to tread in his footsteps may find them. The book makes more fluent reading if these are skipped, since the conclusions of each experiment are briefly stated. The author is particularly to be commended for the clarity with which he has pointed out phenomena other than waxy flexibility by means of which the catatonic state may be recognized. His classification of the phenomena characteristic of catatonia is as follows:

A. Hypokinetic phenomena

   1. Diminished motor initiative

   2. Catalepsy

   3. Negativism
     (*a*) Passive
     (*b*) Active ·

B. Hyperkinetic phenomena

C. Autonomic phenomena

Two tests of particular value for the demonstration of catatonia in man are described, one to bring out a latent catalepsy and the other to test for passive negativism. The patient kneels on one chair and rests his hands on another;

297

then the chairs are gradually separated and the patient is "drawn out," and may remain in this position for a considerable period. In the test for passive negativism, the examiner faces the patient, standing, and without saying what he intends to do slowly rotates the shoulders of the patient 180 degrees or more. If the patient fails to move his feet adequately to compensate for the changed posture, the reaction to the test is positive. Active negativism is noted if the patient when pushed in a certain direction takes several steps in the opposite direction; in passive negativism he may be pushed *en bloc* and remains in the final position.

De Jong seems to be on safer ground when he relies on these tests than when he includes "diminished motor initiative" among the characteristic signs of catatonia. Also, the hyperkinetic phenomena are observed in states other than catatonia. Both these conditions seem to have a fairly definite relation to the functioning of the frontal lobe, but de Jong's experiments do not show that the syndrome of catatonia may be evoked by lesions of the frontal lobe.

New Directions in Psychology: Toward Individual Happiness and Social Progress. By Samuel Lowy, M.D. Price, $3. Pp. 194. New York: Emerson Books, Inc., 1945.

This book, written primarily for laymen, is concerned with one of the major problems facing the world today, namely, the "cultural lag" between modern scientific doctrines and the woefully inadequate use which society makes of them. Using the informal essay style suitable for a nonprofessional reader, Dr. Lowy has written a series of short articles urging the application of modern psychologic technics to social reconstruction. His thesis is that the "core of the social problem is the element of aggression in its various aspects and manifestations." The author uses chiefly freudian concepts, with occasional reference to other psychologic systems.

Dr. Lowy attempts to cover a wide range of topics, varying from politics to marriage, education and religion. In a brief chapter, entitled "Suggestions on General Reform," he advocates a rather nebulous state combining the best features of both communism and democracy without any of their weaknesses. This makes interesting reading but is hardly practical at present, and the subject is dealt with on a very superficial plane. There are certain deficiencies in structure and style which detract somewhat from the effectiveness of the book. Since much of the subject matter is controversial in essence, the parenthetic and apologetic asides which the author intersperses throughout the text serve only to increase the reader's uncertainty in attempting to clarify the issues in his own mind. In addition, the author, in his preface, advises the reader to turn to the "Closing Remarks" first, whereas it would have been more logical to label these "Opening Remarks," placing the text before the first chapter.

Despite these minor weaknesses, the book is stimulating, and Dr. Lowy writes with obvious sincerity and enthusiasm. It is recommended particularly to psychologists, sociologists, educators and enlightened politicians who are interested in the betterment of human relations through a fuller understanding of mental processes.